

## **EXHIBIT A**



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# Enantioselective perception of chiral odorants

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**Abstract**—This review gives an updated account on the phenomena of enantioselective perception of chiral fragrances employed in fine and functional perfumery, and of some selected flavours. Differences between enantiomers both in odour quality and strength have been considered.

*“Il est des parfums frais comme des chairs d’enfants,  
doux comme les hautbois, verts comme les prairies,  
—et d’autres, corrompus, riches et triomphants,  
ayant l’expansion des choses infinies  
comme l’ambre, le musc, le benjoin et l’encens,  
qui chantent les transports de l’esprit et des sens”*

(C. Baudelaire, *Les Fleurs du Mal, Correspondances*)

*“The perfume is as fresh as the flesh of an infant,  
Sweet as an oboe, green as a prairie,  
—And the others, corrupt, rich and triumphant,  
Enlightened by the things of infinity,  
Like amber, musk, benzoin and incense,  
That sing, transporting the soul and sense”*

(translated by William A. Sigler)

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## 1. Introduction

Last year a review appeared in *Enantiomer*<sup>1</sup> describing the challenges of detecting chirality on Titan, Saturn's largest moon. Scientists are indeed planning to send there a robotic analyser that will perform detailed studies of Titan's atmosphere, surface and oceans. Among the analytes to be detected are enantiomerically enriched organic compounds. Enantioenrichment is considered a signal of that chemical complexity which is fundamental for Life. The resemblance of Titan's environment to that of prebiotic Earth leads researchers to believe that the organic world of Titan bears clues to how life on Earth began.<sup>2</sup>

Life and chirality are strictly connected.<sup>3</sup> It is generally recognised that enantiomers may show different behaviour when interacting with living beings. The enantiomers of chiral drugs are often characterised by different pharmacological activity,<sup>4</sup> and the 'chiral switch' procedure has been widely developed by the pharmaceutical industry. In 2001, of the \$410 billion in worldwide sales of formulated pharmaceutical products, \$147 billion (36%) was due to single enantiomer drugs.<sup>2</sup>

Chiral pheromones are employed by animals as communication substances: one enantiomer is usually bioactive, whereas the other one is either inactive or inhibitory.<sup>5</sup> The (*S*) enantiomer of japonilure **1**, the female sex pheromone of the Japanese beetle (*Popilla japonica*), strongly inhibits the activity of (*R*)-**1**.<sup>6</sup> (+)-*exo*-Brevicomin **2** shows activity as the aggregation pheromone of the western pine beetle (*Dendroctonus brevicomis*), while the (–)-enantiomer is completely inactive.<sup>7</sup> Enantiomeric molecules can be distinguished by taste: amino acids of the *L*-series are usually bitter, while those of the *D*-series are sweet.<sup>8</sup>

In 1961 Ohloff<sup>9</sup> published the first data regarding the enantioselective perception of chiral odorants: (+)-β-Citronellol **3** was described to have a typical citronella odour, while (–)-**3** was found of geranium type. Other classical examples of enantiomers showing different odour properties are reported in Table 1.

Enantiomers can differ either in odour quality, i.e. they can elicit different odour sensations, or in odour intensity. This latter property can be described by the value of the odour threshold, i.e. 'the lowest odorant concentration in air that can be consistently distinguished from pure air'.<sup>17</sup> The odour threshold value can be expressed in terms of the weight of odorant per unit volume of air as determined by olfactometry, or determined in solution according to Guadagni's procedure<sup>18</sup> or to the triangular test.<sup>19</sup>

Many theories<sup>20,21</sup> have been developed to explain how an odorant generates a particular signal that is interpreted by the brain as an odour, but none of them has

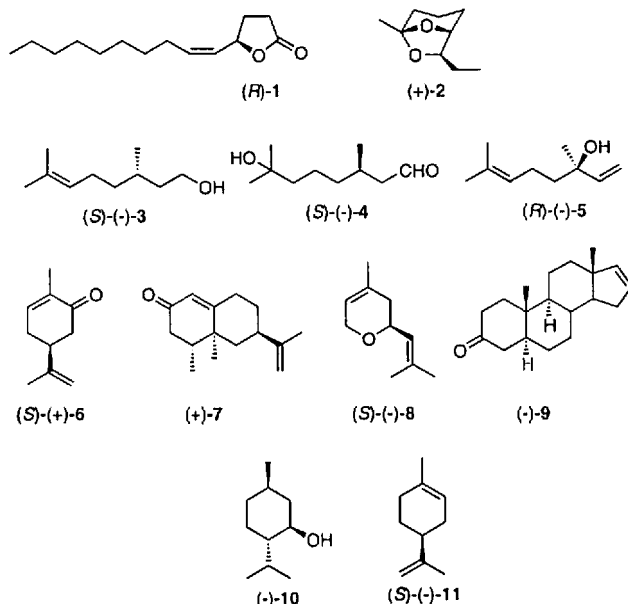
been able to explain all the experimental evidence.<sup>†</sup> Enantiomers have been used as very efficient probes to investigate the olfactory transduction process, and, in particular, to verify how molecular structure is encoded by the olfactory system.<sup>22</sup> With non-enantiomeric odorants, response differences can be partially due to properties (such as the odorant's diffusion rate in the mucus or its air/mucus partition coefficient) determining differential effects before the real interaction with the olfactory receptor. It is well established that enantiomers exhibit the same chemical physical properties, thus any odour perception difference must originate from chiral selectivity at the peripheral level.<sup>22</sup> Even if the receptor molecules, e.g. the membrane proteins, are chiral, it may happen that the interaction with a chiral odorant is not 'enantioselective', when, for example, the molecule profile presented by the odorant to the receptor does not contain the stereogenic elements of the chiral molecule. Recent studies performed on rodents

**Table 1.** Classical example of enantiomers showing different odour properties

Compound	Odour description
7-Hydroxy-6,7-dihydro-citronellal <b>4</b> <sup>10</sup>	(+): Lily of the valley with green minty notes (–): Sweet lily of the valley note
Linalool <b>5</b> <sup>11</sup>	(+): Sweet, petigrain (–): Woody, lavender
Carvone <b>6</b> <sup>12</sup>	(+): Caraway (–): Spearmint
Nootkatone <b>7</b> <sup>13</sup>	(+): Grapefruit (–): Woody, spicy
Nerol oxide <b>8</b> <sup>14</sup>	(+): Green, floral (–): Green, spicy, geranium
Androstene <b>9</b> <sup>15</sup>	(+): Odourless (–): Sweaty, urine, strong, musky
Menthol <b>10</b> <sup>16</sup>	(–): Sweet, fresh, minty, strong cooling effect (+): Dusty, vegetable, less minty, less cooling
Limonene <b>11</b> <sup>12</sup>	(+): Orange (–): Turpentine

<sup>†</sup> In humans, odorants are detected by the olfactory epithelium, which is located at the top of the nasal cavity. Nerve signals are transmitted from the epithelium to the olfactory bulb through the cribriform plate, and then to the limbic system and the higher brain. The neurons from the epithelium converge on areas of the olfactory bulb known as glomeruli. It seems that all the signals from one type of receptor converge on the same glomerulus. Odorants from the air enter the mucus layer around the receptor cells in the epithelium. The interaction of the odorant with the receptor protein, located in the lipid mucosa of the cells, is able to produce a change in the conformation of the latter. This change causes the G-protein associated with the receptor to activate either phospholipase-C or adenylyl cyclase. In the former case the second messenger is inositol triphosphate and in the latter it is adenosine monophosphate. Both are released into the cell and cause calcium ion channels to open in the cell membrane and thus generate nerve signals.

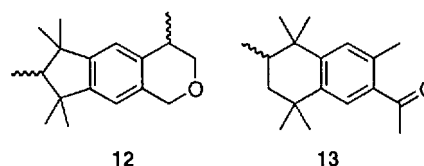
by using the technique of optical imaging have revealed the spatial distribution of odorant responsiveness in the brain.<sup>23</sup> Odorants with different functional groups were found to activate distinct domains in the olfactory bulb. Uchida et al.<sup>23c</sup> performed a systematic investigation of olfactory stimuli, and found that aldehydes and organic acids elicited overlapping activity within an anteromedial region, while alcohols and certain ketones activated a more lateral region. Rubin and Katz<sup>23b</sup> reported that rats can readily distinguish the enantiomers of carvone, like humans and nonhuman primates, and, in contrast to humans, those of fenchone, 2-butanol, and 2-octanol. In all cases the tested enantiomers elicited overlapping but readily distinguishable patterns of glomerular activation in the dorsal rat olfactory bulb, with one or more glomeruli responding preferentially to a particular enantiomer. These data may suggest that enantiomer discrimination results from the activation of certain distinct glomeruli.<sup>24</sup>



The odorants we smell in our daily life are usually fragrances, employed in fine and functional perfumery, and flavours, already contained or added into food and beverages.

**Fragrances.** Perfumers are continuously asking for new synthetic compounds evoking unusual and stimulating odour sensations or reproducing those elicited by natural fragrances. Chemists have, therefore, devoted great effort to investigate the odour properties of enantiopure chiral fragrances, in order to define the structural parameters necessary for evoking a certain odour impression, and to establish odour-structure relationships helpful in satisfying this request. A further aspect of this research is related to the increasing environmental and health risks associated with massive usage of fragrances in fine and functional perfumery.<sup>25</sup> Certain polycyclic musks were found to contaminate waterways and aquatic wildlife,<sup>26</sup> and were also iden-

tified in human adipose tissue and human milk.<sup>27</sup> It has also been shown that stereoisomers can accumulate selectively in living beings. The four stereoisomers of Galaxolide<sup>®</sup> 12 were found in crucian carp (*Carassius carassius*) in the ratio 0.1/0.3/0.6/1, while the two enantiomers of Tonalide<sup>®</sup> 13 were identified in tench (*Tinca tinca*) in 0.5:1 ratio.<sup>28</sup> If only the odour active isomers are employed in commercial products, the toxicological risks connected with the exposure to chemicals present in perfumed articles could be reduced. Thus, for old and new fragrances the identification of the isomer acting as the main odour vector has become an unavoidable task. Within this extensive investigation, interesting examples of enantioselectivity in the odour perception of chiral fragrances for perfumery applications have been found and are described in this review.



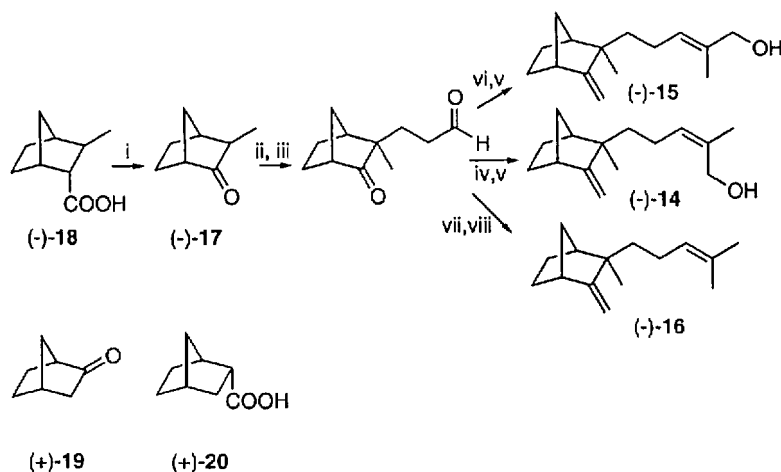
**Flavours.** Compounds to be added to food and beverages are subjected to strict regulations and are usually natural or nature-identical. The choice of the best 'aromatic' isomer is up to Nature: most of chiral natural flavours occur in enantiomerically enriched form. Chemists have systematically investigated the absolute configuration of natural flavours, and tried to establish a correlation between cultivar or geographic origin, and the enantiomeric excess of a certain aroma.<sup>29</sup> This work has allowed the optimisation of analytical methods for the assessment of authenticity of natural materials. Mosandl reported,<sup>30</sup> for example, the usefulness of enantioselective capillary GC analysis in the authenticity control of malic acid. While racemic malic acid is allowed as a souring additive in Mediterranean table wines, the detection of racemic malic acid in fruit juices, nectares, and other foods should be interpreted as falsification.

In this review only a brief overview is given on the different odour response of enantiomeric chiral flavours, as this topic is as wide as the natural world.

There have been previous reviews on the enantioselective perception of chiral odorants<sup>31</sup> and exhaustive discussions on synthetic methods and on the optimisation of structure-odour relationships for the rational design of odorants.<sup>32–34</sup>

## 2. Woody and amber odorants

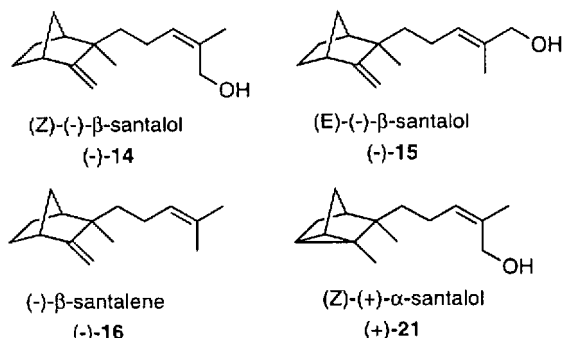
"Who is this that makes her way up by the desert road, erect as a column of smoke, all myrrh and incense, and those sweet scents the perfumer knows?" (The Song of Songs 3, 6)



**Scheme 1.** Reagents and conditions: (i) LDA, DMPU,  $O_3$ ,  $P(OEt)_3$ ;  $LiAlH_4$ , THF;  $NaIO_4$ , water, EtOH; (ii)  $NaN(SiMe_3)_2$ , xylol; (iii)  $H_3O^+$ ; (iv)  $(EtO)_2OPCH(CH_3)COOEt$ ,  $KN(SiMe_3)_2$ , 18-crown-6; (v)  $CH_2Br_2$ , Zn,  $TiCl_4$ ; DiBAH,  $CH_2Cl_2$ ; (vi)  $Ph_3PC(CH_3)COOEt$ , THF; (vii)  $Ph_3PCHMe_2Br$ ,  $NaNH_2$ , THF; (viii)  $CH_2Br_2$ , Zn,  $TiCl_4$ .

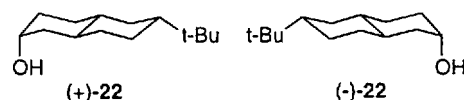
## 2.1. Sandalwood<sup>35</sup>

East Indian Sandalwood oil, obtained from the tree *Santalum album* L. Santalaceae, is a complex mixture of ingredients, widely employed in perfume compositions because of its warm woody odour. It is difficult to establish the contribution of each component to the overall odour profile.<sup>36</sup> (*Z*)-(-)- $\beta$ -Santalol **14**, which represents approximately 25% of the oil weight, is considered to be the main sandalwood odour vector, and it is described as *lactonic, floral, woody, milky and musky*.<sup>32a</sup> The two enantiomers of **14** were prepared in enantiomerically pure form,<sup>37</sup> together with the enantiomers of (*E*)- $\beta$ -santalol **15**, and  $\beta$ -santalene **16**, minor constituents of natural sandalwood oil. The synthetic sequence (Scheme 1) to the enantiomers of **14–16** was based on the stereoselective *exo* alkylation of enantiomerically pure 3-methyl-2-norbornanones (+)- and (-)-**17**. Compound (-)-**17** was prepared by oxidative degradation of the corresponding norbornane carboxylic acid (-)-**18**. (+)-**17** was obtained by alkylation of (+)-2-bornanone **19**, prepared from (+)-**20**, according to the same procedure described for the conversion of (-)-**18** into (-)-**17**. (-)-**14** was found to show the typical sandalwood scent, identical to that of natural **14**, while the (+)-enantiomer was described as *odourless*. (-)-**15** developed a scent similar to (-)-**14**, but less intense. (+)-**15**, (+)-**16** and (-)-**16** were *odourless*.

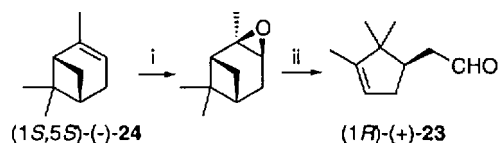


(*Z*)-(+)- $\alpha$ -Santalol **21**, which is about 45–47% of natural sandalwood oil, was reported to be *more woody and cedarwood* than (-)-**14**, but its contribution to sandalwood odour is controversial.<sup>32a</sup>

*t*-Butylbicyclo[4.4.0]decan-3-ol **22**<sup>38</sup> is a synthetic compound showing a typical sandalwood fragrance, and is usually employed as a standard for molecular calculations and surface comparisons of sandalwood odour molecules, thanks to its rigid structure. The olfactory properties of its enantiomers have been described. Racemic **22** was resolved via fractional crystallisation of the diastereoisomeric ephedrine salts of the corresponding phthalic acid half ester. The fragrance of (+)-**22** was described as *strong, sandalwood like, warm, sweet, and long persisting*, whereas the scent of (-)-**22** appeared *very weak, fatty, hardly perceptible, with remote animalic notes*.



Among the synthetic chemicals developed to satisfy the demand for sandalwood odour, the derivatives of campholenaldehyde **23** are the most diffuse and appreciated. The enantiomers of **23** are readily prepared from (-)- and (+)- $\alpha$ -pinene **24**, via epoxidation and  $ZnBr_2$  treatment<sup>39</sup> (Scheme 2). For several derivatives of cam-

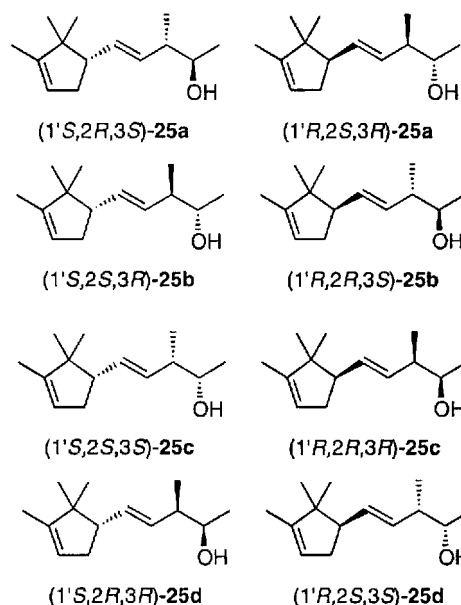


**Scheme 2.** Reagents and conditions: (i) 3-chloroperbenzoic acid,  $CH_2Cl_2$ ,  $NaHCO_3$ ; (ii)  $ZnBr_2$ , benzene.

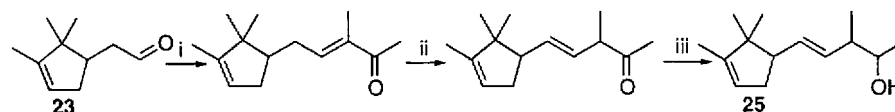
phenolic aldehyde the olfactory properties of each enantiomer are known to be quite different.

**Ebanol**<sup>®</sup>.<sup>40</sup> In 1986 Naipawer described Ebanol<sup>®</sup> **25** as a relevant sandalwood odorant showing a *tenacious fine soft woody odour similar to sandalwood oil*. The compound was prepared as a mixture of four racemic diastereoisomers **25a–d** starting from campholenic aldehyde **23**, according to Scheme 3. Spinning band distillation allowed the separation of two fractions, each one being a mixture of two racemic diastereoisomers. The lower boiling fraction **I** was shown to contain (1'*RS*,2*SR*,3*RS*)-**25a** and (1'*RS*,2*RS*,3*SR*)-**25b**, while the higher boiling fraction **II** was a mixture of (1'*RS*,2*RS*,3*RS*)-**25c** and (1'*RS*,2*SR*,3*SR*)-**25d**. The relative configuration within the stereoisomers was established by <sup>1</sup>H NMR analysis and by X-ray diffraction studies on suitable crystalline derivatives. Fraction **I** was designated as the campholenic aldehyde derivative having the strongest odour ever reported. Its odour threshold (GC olfactometry) was about 500 times lower than that of fraction **II**. These data showed the great influence of relative configuration on the odour properties of a compound. The complete olfactory evaluation of all the eight enantiopure isomers of Ebanol was performed by Bajgrowicz and Frater by the chiral GC-sniff technique.<sup>41</sup> Naipawer's synthetic procedure was repeated starting from (+)- and (–)-**23**, to afford two mixtures each of four enantiopure diastereoisomers. Stereoisomers (1'*S*,2*S*,3*R*)-**25b** and (1'*R*,2*S*,3*R*)-**25a** turned out to be the vectors of the strong natural sandalwood odour of the mixture. The odour intensity ratio of these two stereoisomers was ~3–5:1. Their odour was by far the strongest and they were apparently the only ones of the eight stereoisomers to show a *natural, warm, lactonic sandalwood type of odour*. Thus, the absolute configuration of the stereogenic centres C(2) and C(3) in the side chain plays a key role in the

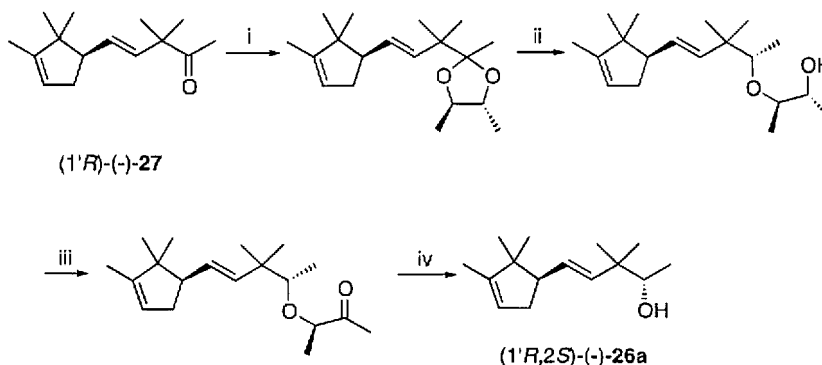
perception of sandalwood odour, and is more important than that of the stereocentre in the carbocycle.



**Polysantol**<sup>®</sup>.<sup>42</sup> The four stereoisomers of Polysantol<sup>®</sup> **26a,b** were prepared with an enantiomeric excess of at least 90%. Further purification by fractional crystallisation of the corresponding dinitrobenzoate esters could be achieved. According to Scheme 4, (1'*R*)- and (1'*S*)-**27** reacted separately with both (–)- and (+)-butanediol, and gave acetal derivatives which were then submitted to stereoselective reduction to give key intermediates for the preparation of (1'*R*,2*S*)-**26a** and (1'*R*,2*R*)-**26b**, (1'*S*,2*S*)-**26b** and (1'*S*,2*R*)-**26a**, respectively. In Scheme 4, reaction of (1'*R*)-**27** with (–)-butanediol to afford (1'*R*,2*S*)-**26a** is illustrated. The four isomers were also obtained by enzymatic hydrolysis of the chloroacetate

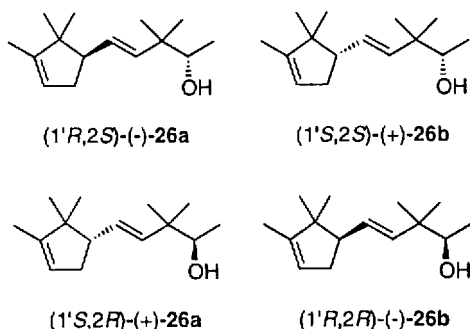


**Scheme 3.** Reagents and conditions: (i) butan-2-one; (ii) *t*-BuOK, DMF; (iii) NaBH<sub>4</sub>, EtOH.



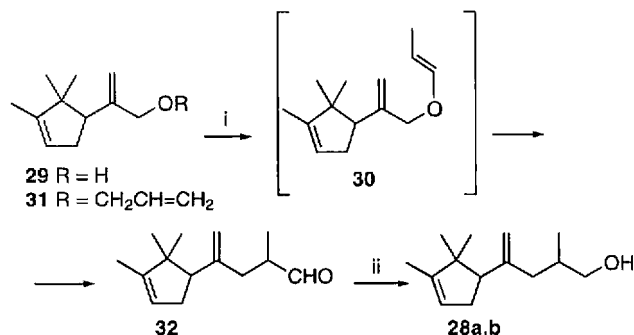
**Scheme 4.** Reagents and conditions: (i) (–)-butanediol; (ii) LiAlH<sub>4</sub>, AlCl<sub>3</sub>, Et<sub>2</sub>O; then column chromatography; (iii) PCC, CH<sub>2</sub>Cl<sub>2</sub>; (iv) Na, Et<sub>2</sub>O.

esters of the two mixtures of enantiomerically enriched (1'S,2R*S*)- and (1'R,2R*S*)-Polysantol® diastereoisomers.



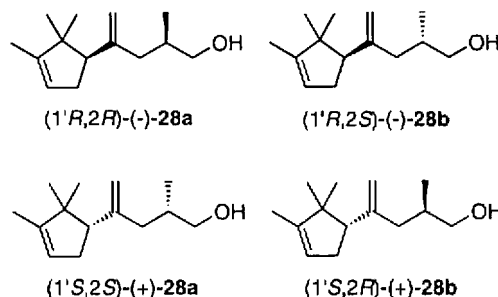
The olfactory evaluation of these samples gave the following results: nine perfumers were unanimous in their preference for (1'S,2*S*)-26b, whose sandalwood odour was judged *remarkably powerful and elegant, with a prized sandalwood milky character*. The (1'R,2*S*)-26a isomer was classed in second place by five out of eight perfumers, its sandalwood note being judged *weaker than that of (1'S,2*S*)-26b, but still very powerful*. The other three perfumers preferred (1'S,2*R*)-26a. According to eight perfumers the (1'R,2*R*)-26b was the least interesting isomer. The ninth perfumer, who generally had some anosmia for the sandalwood note, could only smell (1'S,2*S*)-26b.

**2-Methyl-4-(2',2',3'-trimethyl-3'-cyclopenten-1'-yl)-4-penten-1-ol 28a.**<sup>43</sup> According to Scheme 5, optically active propenols **29**, prepared starting from the enantiomers of campholenic aldehyde, were useful intermediates in the preparation of the four stereoisomers of compound **28**. The key step was the Claisen rearrangement of vinyl allyl ether **30**, obtained by isomerisation of unsymmetrical diallyl ether **31**, to afford  $\gamma$ -unsaturated aldehyde **32**. The two mixtures of enantiomerically enriched diastereoisomers **28a,b** were separated by preparative GC. Stereoisomer (1'R,2*R*)-28a was the most appreciated by the perfumers for *its sandalwood fine and intense odour*: diastereoisomer (1'R,2*S*)-28b was found to show a *less sandalwood odour, with a marked boise-cedre character*. Both of them were described as

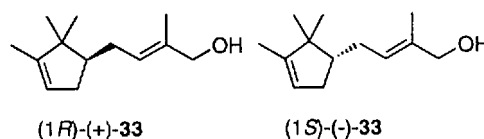


Scheme 5. Reagents and conditions: (i) RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>, 180°C; (ii) NaBH<sub>4</sub>.

having more valuable odour properties than the corresponding enantiomers. (1'S,2*S*)-28a and (1'S,2*R*)-28b were found less rich in the sandalwood character.

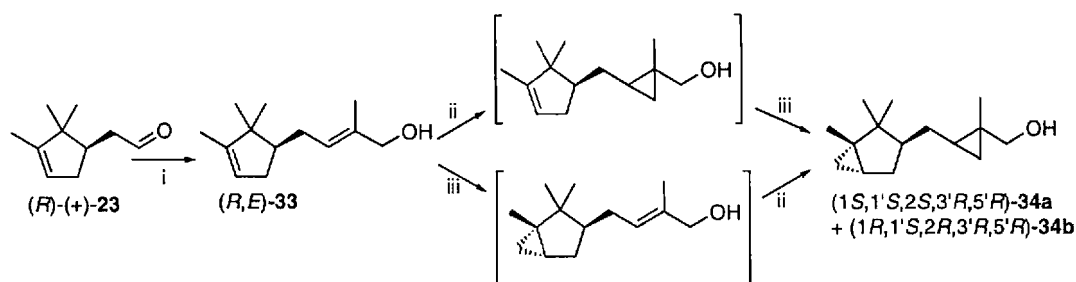


**Madrol® (33)** combined a powerful sandalwood odour with a sweet note. The stereoselective synthesis of (+)- and (-)-**33** was performed by aldolic condensation of (+)- and (-)-campholenic aldehyde **23** with propionic aldehyde, and subsequent reduction.<sup>44</sup> (*S*)-(-)-**33** was described exerting a *powerful sandalwood odour with animalic undertones*, while (*R*)-(+)-**33** smelled *sweet and flowery, of rose type, rather than sandalwood*.



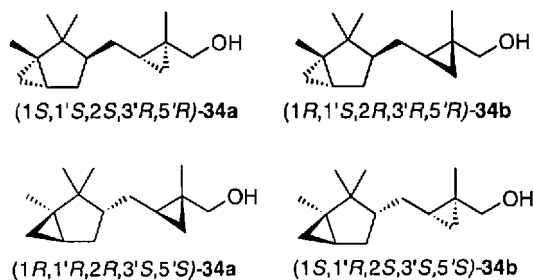
**Javanol® (34).**<sup>45</sup> During their studies on the structure–odour relationship in the woody/amber/sandalwood odorants, Bajgrowicz et al. substituted C=C bonds in a series of derivatives of  $\alpha$ -,  $\beta$ -,  $\gamma$ -campholenic aldehydes by the isoelectronic cyclopropane ring. One of the compounds thus prepared, derivative **34** (Javanol®), showed an exceptionally natural sandalwood-odour profile, and one of the lowest odour thresholds amongst all commercial odorants. The authors investigated which of the possible stereoisomers represented the main odour vector: (1*R*)- and (1*S*)- $\alpha$ -pinenes of the highest commercially available ee (97%) were employed to prepare the two enantiomers of campholenic aldehyde. Condensation with propionic aldehyde and reduction gave the two enantiomers of **33** (Scheme 6). As the cyclopropanation of cyclopentene ring of compound **33** was highly diastereoselective, two mixtures of enantiopure diastereoisomers were made available for olfactory evaluation by the chiral GC/sniff technique. The following results were obtained: (1*S*,1'*S*,2*S*,3'*R*,5'*R*)-34a *sandalwood, creamy, warm, strong* (odour threshold = 0.015 ng<sup>4</sup>); (1*R*,1'*S*,2*R*,3'*R*,5'*R*)-34b *lactonic* (odour threshold  $\geq 15$  ng); (1*S*,1'*R*,2*S*,3'*S*,5'*S*)-34b *floral, rosy, milky, sandalwood* (odour threshold = 0.51 ng); (1*R*,1'*R*,2*R*,3'*S*,5'*S*)-

<sup>4</sup> These GC odour threshold values in ng correspond roughly to the olfactometer odour thresholds in ng/l of air.



**Scheme 6.** Reagents and conditions: (i) EtCHO, MeONa; then NaBH<sub>4</sub>; (ii) CH<sub>2</sub>Br<sub>2</sub>, Zn, CuBr, AcBr, or ultrasound; (iii) CH<sub>2</sub>I<sub>2</sub>, Et<sub>3</sub>Al.

**34a** lactonic, lily of the valley (odour threshold  $\geq 1.4$  ng).



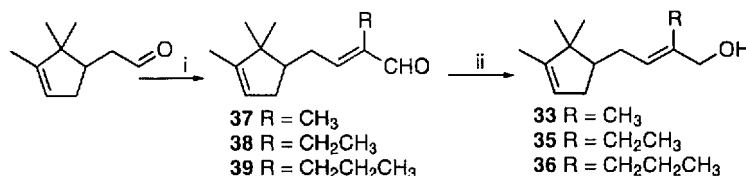
The odour threshold values were found to depend dramatically on the absolute configuration of the cyclopropane moiety linking the *osmosphoric* OH group to the lipophilic, bulky part of the molecule. Thus, the stereochemistry in the neighbourhood of the osmosphoric group is relevant for the sensory properties of this type of substrates.

2-Alkyl-4-(2,2,3-trimethylcyclopent-3-en-1-yl)-2-buten-1-ols **33**, **35** and **36**.<sup>46</sup> In 1997 a patent was filed by

Takasago describing the superior sensory properties of (*E*)-(*R*)-2-alkyl-4-(2,2,3-trimethylcyclopent-3-en-1-yl)-2-buten-1-ols when compared with the (*S*)-enantiomers. Both the enantiomers of campholenic aldehyde were submitted to aldol reaction to afford aldehydes **37**, **38** and **39** (Scheme 7). These latter derivatives were hydrogenated in the presence of a base, an amine and a ruthenium–phosphine complex catalyst, to give enantiopure isomers of **33**, **35**, and (*R*)-**36**. The results of this investigation are reported in Table 2.

No great variation of the sensory properties of compound (*E*)-(*R*)-**35** was observed when the enantiomeric excess of the starting  $\alpha$ -pinene, and consequently of the final compound itself, varied from 50% (economically more advantageous) to 98% (Table 3).

The results for Madrol® (**33**) were opposite to those reported by Buckbauer et al.<sup>44</sup> In 2001 Mosandl and Bilke<sup>47</sup> repeated the enantioselective synthesis of the two enantiomers of Madrol®, and submitted them to sensory evaluation (10 ppm in dipropylene glycol). The (*R*)-enantiomer was found to possess a strong sandal-



**Scheme 7.** Reagents and conditions: (i) RCHO, MeONa; (ii) H<sub>2</sub>, RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>, 1,3-diaminopropane, KOH, isopropanol.

**Table 2.** Sensory evaluations of compounds **33**, **35** and **36**

Compound	Odour description	Odour threshold (10 <sup>-12</sup> M/l)	Optical purity (%)
( <i>E</i> )-( <i>R</i> )- <b>33</b>	Fresh and strong sandalwood oil odour associated with green trees	51	97
( <i>E</i> )-( <i>S</i> )- <b>33</b>	Dry and weak sandalwood oil odour with a milky and floral note	424	97
( <i>E</i> )-( <i>R</i> )- <b>35</b>	Clean, bright and strong sandalwood oil odour with richness and a woody note	0.85	97
( <i>Z</i> )-( <i>R</i> )- <b>35</b> <sup>a</sup>	Inferior to the <i>trans</i> compound in strength, lacking a woody note, and having butter-like sweetness	Not determined	97
( <i>E</i> )-( <i>S</i> )- <b>35</b>	Milky sandalwood oil odour with a cedar character	44	97
( <i>E</i> )-( <i>R</i> )- <b>36</b>	Soft and warm sandalwood oil odour, slightly weaker than ( <i>E</i> )-( <i>R</i> )- <b>35</b>	Not determined	97

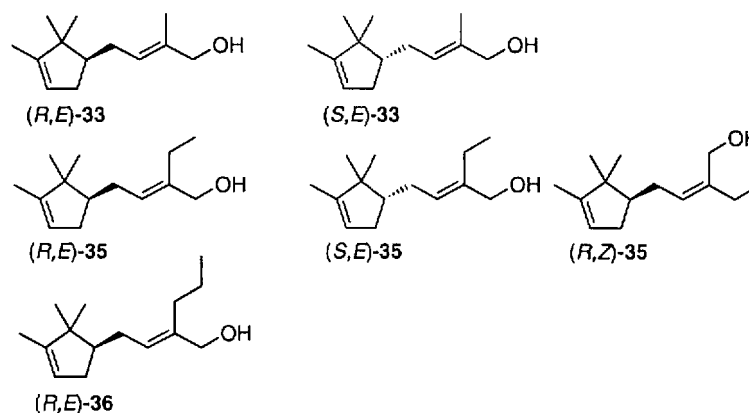
<sup>a</sup> Obtained as a by-product during the preparation of the corresponding (*E*)-isomer.



**Table 3.** Sensory properties of derivative (*R*)-35 as a function of enantiomeric excess

Compound	Enantiomeric excess (%)	Odour description
(E)-( <i>R</i> )-35	97	Strong, clear, warm and creamy odour primarily having a woody note inherent to natural sandalwood
	92	Strong, clear, warm and creamy odour primarily having a woody note inherent to natural sandalwood
	80	Strong, clear, warm and creamy odour primarily having a woody note inherent to natural sandalwood
	70	Strong odour having a woody note inherent to natural sandalwood, slightly associated with green trees
	60	Strong odour having a woody note inherent to natural sandalwood, slightly associated with green trees
	50	Sandalwood oil odour, while slightly astringent compared with the previous samples
	40	Sandalwood oil odour as in the previous examples, but lacking clearness with increased cedarwood-like astringency and sweetness
Bacdanol <sup>®</sup> <sup>a</sup>	( <i>S</i> )-40%	Less sandalwood-like than all the other samples

<sup>a</sup> Commercially available (from IFF) 2-ethyl-4-(2,2,3-trimethylcyclopent-3-en-1-yl)-2-buten-1-ol (*R*)/(*S*) = 30/70.



wood-like odour, whereas the (*S*)-isomer showed a faint milky odour. In the same work a useful method for the enantioselective analysis of  $\alpha$ -campholenic aldehyde and Madrol<sup>®</sup> was achieved by enantioselective GC using *tert*-butyldimethylsilylated-cyclodextrin derivatives as chiral GC phases.

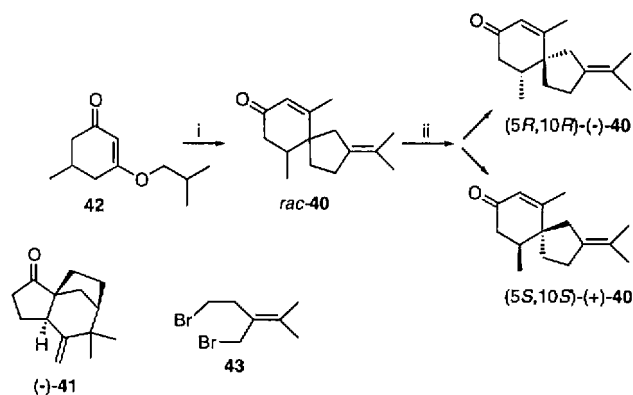
The analysis of the sensory data of the sandalwood odorants derived from campholenic aldehyde suggests that the geometry of the immediate proximity of the osmophoric hydroxy group tolerates less variations than the more distant lipophilic bulky group.

The knowledge of the exact configuration of the best odour vectors should allow the definition of the sandalwood olfactophore model for a more rational design of still better sandalwood odorants.<sup>48</sup> Small structural changes may influence the physical properties and consequently the final concentration at the receptor site. Thus, it may be hazardous to draw conclusions from quantitative olfactory responses even within a family of similar molecules. This drawback can be attenuated by comparison between enantiomers, assuming an equal concentration at the receptor site. For example, Chapuis refined his structure–odour model for sandalwood odorants using the olfactory comparison of more than 120 enantiomeric pairs.<sup>49</sup>

## 2.2. Vetiver and patchouli

Vetiver oil<sup>50</sup> possesses a strong sweet woody odour, with earthy, green, fungi-type aspects and grapefruit, rhubarb

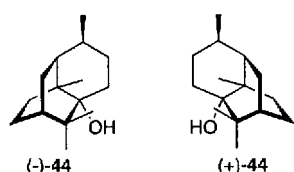
undertones.<sup>32b</sup> It is isolated from the clean dried rootlets of the grass *Vetiveria zizanoides* by steam distillation. It has not been established yet which is the component which mainly contributes to this scent, as several controversial evaluations were reported on some of the constituents, such as  $\beta$ -vetivone 40 and khusimone 41.<sup>51–53</sup> In 1998 Spreitzer et al.<sup>54</sup> prepared the two enantiomers of  $\beta$ -vetivone, according to Scheme 8. Enol ether 42 underwent spirocyclisation with dibromide 43 to give, after treatment with MeLi and acidic work-up, racemic 40. The resolution was carried out by reaction with lithiated (*R*)-(-)-*N,S*-dimethyl-*S*-phenylsulphoximine, which afforded MPLC



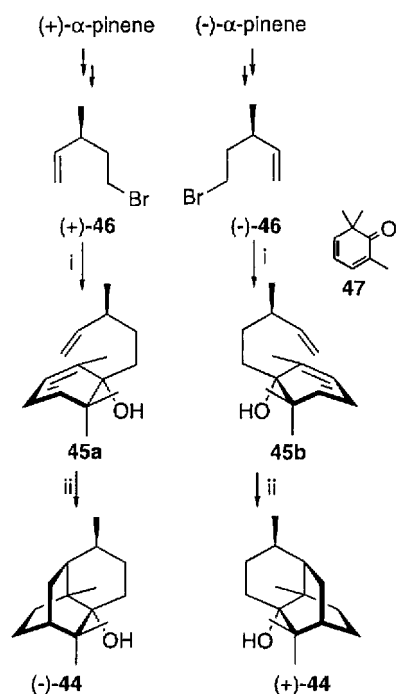
**Scheme 8.** Reagents and conditions: (i) dibromide 43, THF, DMPU; then MeLi, H<sub>3</sub>O<sup>+</sup>; (ii) (*R*)-(-)-*N,S*-dimethyl-*S*-phenylsulphoximine, BuLi; separation of diastereoisomeric adducts via MPLC, then reflux in toluene.

separable mixtures of diastereoisomeric sulfoximine adducts. These adducts were separated and submitted to thermolysis in refluxing toluene to yield enantiomerically pure (+)- and (–)-40. Differences were found in the odour quality of the two enantiomers: (–)-40 was found to be *quinoline like, reminiscent of cassia and grapefruit*, and (+)-40 exhibited an *unpleasant cresolic, medicinal note*. None of them possessed the pleasant vetiver scent.

Selectivity was also noted in the perception of the enantiomers of patchoulol 44, the compound which is fundamental for the odour of the essential oil obtained from patchouli. This latter is a small shrub (*Pogestemon cablin* Benth.) cultivated in India, the Philippines, Java, Sumatra and Singapore, and it gives an essential oil which develops a *powerful, woody-balsamic odour, with herbaceous, earthy, camphoraceous, and floral nuances*.<sup>32b</sup>



The stereoselective synthesis of (+)- and (–)-patchoulol was carried out by Näf et al. in 1981 (Scheme 9).<sup>55</sup> The key step was the diastereoselective intramolecular Diels–Alder reaction of optically active trienols 45a and 45b. These latter derivatives were prepared by reaction of cyclohexenone 47 with the lithium derivatives obtained by treatment of (+)- and (–)-46 with lithium. Nature-identical (–)-44 was found to exhibit a strong, typical patchouli

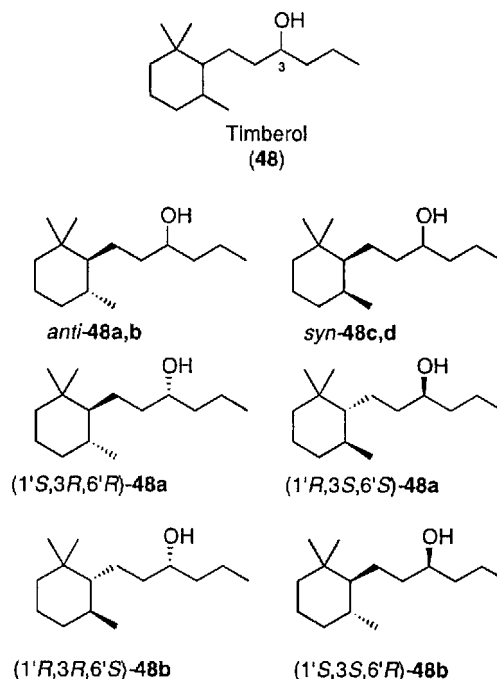


**Scheme 9.** Reagents and conditions: (i) Li, compound 47; (ii) 280°C, *t*-BuOK, *p*-xylene (sealed Pyrex tube).

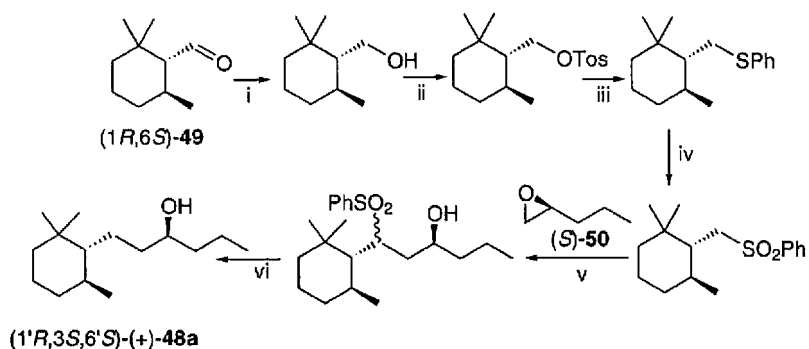
scent with an earthy, slightly camphoraceous, powdery cellar note which was indistinguishable from natural patchouli alcohol. (+)-44 was found to be much weaker, less characteristic, nearly indefinable and by no means reminiscent of patchouli. It might have a  $\beta$ -santalol odour with a green undertone. The odour of racemic 44 was described to be simply a blend of both enantiomers the contribution of the nature-identical one being greater.

### 2.3. Timberol®

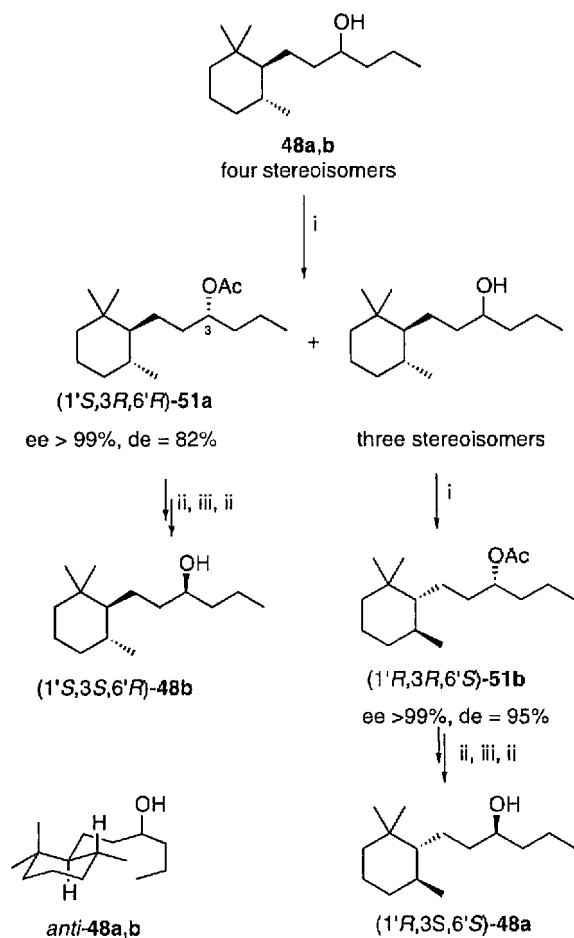
1-(2,2,6-Trimethylcyclohexyl)-3-hexanol 48 represents an interesting case of diastereoselectivity and enantioselectivity in odour perception. It was introduced by Dragoco<sup>56</sup> as a synthetic fragrance with fixative properties with the brand name Timberol®. Commercial Timberol® was mainly composed by four racemic diastereoisomers 48a–d and showed a *powdery-woody odour with animal, steroid-type undertones*. It was soon established that the woody animal note was due to the *anti*-diastereoisomers 48a,b.<sup>57</sup> The 1:1 mixture of the two racemic *anti*-diastereoisomers 48a and 48b was then prepared, and commercialised by Firmenich with the brand name of Norlimbanol®.



The single enantiomers of 48a and 48b were synthesised, starting from (1*R*,6*S*)- and (1*S*,6*R*)-dihydrocyclocitral (49) and (*R*)- and (*S*)-2-propyloxirane 50<sup>58</sup>, as shown in Scheme 10. The olfactory evaluation of (+)- and (–)-48a and of (+)- and (–)-48b gave the following results. (1'*R*,3*S*,6'*S*)-(+)-48a was described as the best of the series, *powerful and long-lasting, with a very nice woody-ambery note*. (1'*S*,3*S*,6'*R*)-(–)-48b showed an odour note resembling that of (1*R*,3*S*,6'*S*)-(+)-48a, but less powerful and decidedly inferior. The (3*S*) isomers were devoid of the animal character and very weak.<sup>58,59</sup> A few years ago we submitted the mixture of the four stereoisomers of 48a,b to enzymic acetylation<sup>60</sup> (Scheme 11). (3*R*)-Acetate 51a was first obtained (24 h reaction time). After 7 days (3*R*)-acetate 51b was recovered. Hydrolysis of (3*R*)-51a



**Scheme 10.** Reagents and conditions: (i) NaBH<sub>4</sub>; (ii) *p*-toluenesulphonyl chloride; (iii) C<sub>6</sub>H<sub>5</sub>SH, K, EtOH; (iv) *m*-chloroperbenzoic acid; (v) BuLi, THF; HMPT, BF<sub>3</sub>; (vi) Li–Naphthalene, THF; Ac<sub>2</sub>O, Et<sub>3</sub>N; O<sub>3</sub>, hexane; LiAlH<sub>4</sub>, Et<sub>2</sub>O.



**Scheme 11.** Reagents and conditions: (i) Lipase PS, *t*-butyl-methyl ether, vinyl acetate; (ii) KOH, MeOH; (iii) *p*-TosCl, pyridine; AcONa in DMF.

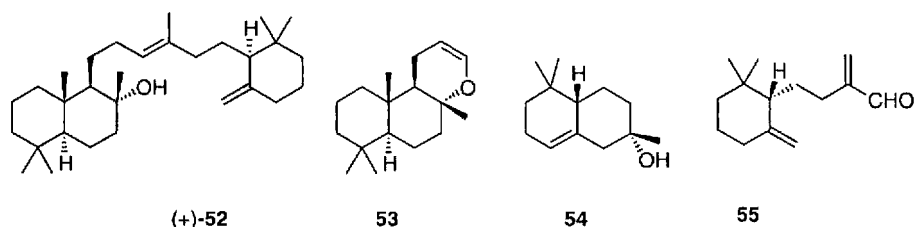
and (3*R*)-51b gave (3*R*)-48a and (3*R*)-48b, respectively. Inversion of the configuration by acetate displacement afforded the corresponding odorous (3*S*)-isomers.

Dextro Norlimbanol<sup>®</sup>, i.e. (1*R*,3*S*,6'*S*)-(+)-48a<sup>61</sup> is just starting to be used in perfumery;<sup>62</sup> it is *velvety, more powerful than Norlimbanol<sup>®</sup>, and suitable to create nice accords with a lot of other fragrances*. The characteristic odour of Timberol<sup>®</sup> is clearly configuration dependent: the specific odour is released when all the substituents are in equatorial position, in a conformation resembling that of odorous steroids.<sup>57</sup>

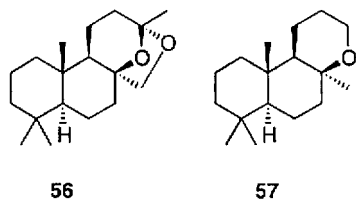
#### 2.4. Amber

Ambergris is a pathological metabolite of sperm whales (*Physeter macrocephalus* L.), and it functions as a cover for the injuries incurred in their intestines as a result of food intake. It has been described<sup>63</sup> as possessing *an exotic-woody, incense-like, earthy, camphoraceous, tobacco-like, musk-like odour, which also smells of the ocean*. Its main component is the odourless derivative (+)-ambrein 52. The odour qualities of ambergris are due to components which are generated from ambrein by exposure to air and sunlight, after the ambergris is expelled by the whale. Simulation of these conditions by treatment of ambrein with singlet oxygen led to the formation of tricyclic enol ether 53, α-ambrinol 54 and amber aldehyde 55.

Ohloff studied intensively the structure-activity correlations in ambregris-type odorants.<sup>63</sup> The main structural features of this group are the presence of a bicyclo[4.4.0]decane (decalin) skeleton carrying at least one alcohol, ether, or ester as osmophoric groups and alkyl substituents at specific positions. However, a compound which fulfils these structural requirements does not



necessarily possess an amber-type odour, and may not even smell at all. As a matter of fact, it has been recognised that within a certain structure, configurational details are also relevant in determining the odour profile and strength. By studying the correlation between diastereoisomerism and ambergris odour in decalin derivatives, Ohloff et al. established the 'triaxial rule' of odour sensation of decalin type compounds.<sup>64</sup> In 1980 Ohloff et al.<sup>65</sup> extensively studied the stereochemistry–odour relationships in enantiomeric ambergris tetra- and tricyclic odorants. For some of these compounds specific anosmia was detected. Compounds **56** and **57** were found odourless according to the triaxial rule, while their corresponding enantiomers were described as possessing a strong odour.

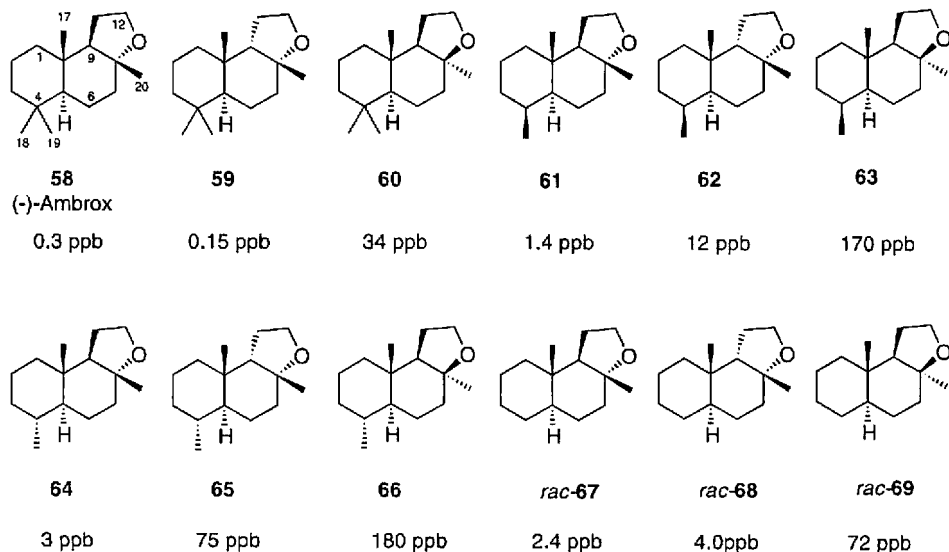


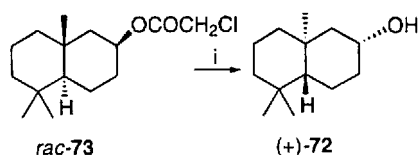
They were presented as the first examples of chiral derivatives for which one enantiomer is completely odourless. A few years later Ohloff studied<sup>66</sup> the significance of the geminal dimethyl group in the odour principle of Ambrox® **58**, one of the most important ambergris-like odorants. He synthesised diastereoisomeric tricyclic ethers **58–60**, the three 18-nor-derivatives **61–63**, the three 19-nor derivatives **64–66**, belonging to the same enantiomeric series. The racemic 18,19-dinor-ethers **67–69** were included in the investigation. All these compounds were submitted to olfactory evaluation. The odour thresholds measured in water are reported under each structure. The threshold data and the odour determinations gave an enlarged insight into the structure–activity in ambrox-type fragrances. (–)-9-Epiambrox **59** possessed the strongest odour and the lowest odour threshold of the series (0.15 ppb). (–)-Ambrox **58** and the nor-derivatives **61** and **62** showed only a small qualitative deviation. Isoambrox **60** showed a remarkable deviation from the model compound Ambrox. Indeed, isoambrox **60** was

found to be a hundred times weaker and 18-norisoambrox **63** five hundred times weaker than Ambrox, according to their threshold values. These results showed that an axial group at C(8) is essential for the receptor event, and confirmed the triaxial rule. Ether **63** only possessed the woody note out of the complex odour profile of Ambrox. No amber note could be perceived in compound **66**, while it was still present in **64** and **65**, although less pronounced than in **61** and **62**. The woody character of Ambrox had not completely disappeared in **67** and **68**, although masked by a more complex odour. Ether **67** was dominated by a earthy odour, reminiscent of freshly ploughed field; ether **68** showed a spicy-woody and grapefruit-like odour, together with exotic flower scents. Compound **69** was musty with a tonality of rotten fruit, completely lacking the amber note. The general conclusion was that the accumulation of axial methyl groups in the tricyclic ethers **58–69** led to the strongest receptor affinity. Compounds **58**, **59**, **61**, and **62** with three axial methyl groups were qualitatively very similar, and exhibited the strongest affinity for the amber odour receptor. Among the nor-derivatives, ethers **61** and **69** showed the greatest quality difference. Compound **66** with two equatorial methyl groups was devoid of the particular ambrox note.

In the same work, the olfactory properties of (+)-Ambrox were reported. (+)-Ambrox with its higher threshold value (2.4 versus 0.3 ppb) and accentuated woody note was found to be lacking the strong and warm animal note of the enantiomer. (+)-Ambrox was, therefore, called 'poor man's ambrox' by Firmenich perfumers. The exotic, spicy note of (+)-Ambrox disappeared in the racemate, for which a threshold value of 0.5 ppb was measured.

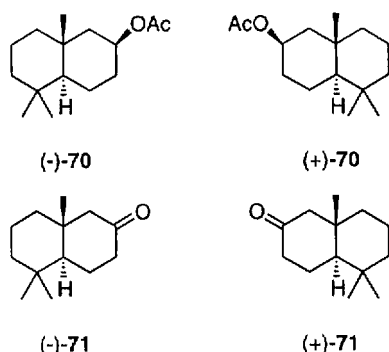
Acetate (±)-**70**, known as Polywood®,<sup>64b</sup> and ketone (±)-**71** are two fragrance chemicals of the woody type. The enantiomeric decahydro-2-naphthalenols (+)- and (–)-**72** were prepared by enantioselective hydrolysis of the racemic chloroacetate (±)-**73** catalysed by porcine pancreatic lipase, and then easily converted into the corresponding acetates (+)- and (–)-**70** and ketones (+)- and (–)-**71** with ee = 95% (Scheme 12).<sup>67</sup> Distinct odour differences were noted between the enantiomers of each pair. Acetate



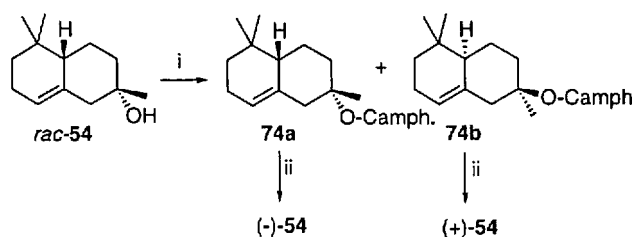


**Scheme 12.** Reagents and conditions: (i) PPL, pH 7.5, 0.1 M potassium phosphate buffer.

(+)-70 was described to exhibit a rich, voluminous woody note with a powdery ionone-like undertone. Conversely, acetate (–)-70 was found less rich, still woody, dry, and amber-like. Ketone (+)-71 was found woody, patchouli-like, and less strong than its enantiomer. (–)-71 was described as strong, woody amber-like, with a distinct note of damp earth, cellar, geosmin.



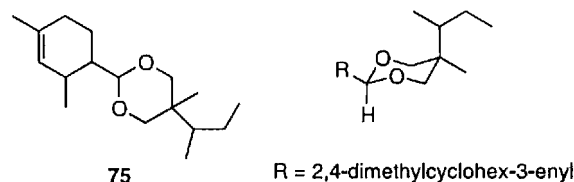
Relevant differences were also found in the olfactory qualities of the enantiomers of another typical ambergris constituent,  $\alpha$ -ambrinol 54.<sup>68</sup> Racemic  $\alpha$ -ambrinol was resolved by fractional crystallisation of the mixture of the two diastereoisomeric 1*S*-(–)-camphanic acid esters 74a and 74b, and subsequent reduction of the chemically pure diastereoisomers (Scheme 13). The two  $\alpha$ -ambrinol enantiomers were obtained with ee = 99.5%. 'Unnatural' (+)- $\alpha$ -ambrinol exhibited a strongly dry earthy, musty tonality, reminiscent of geosmine. The natural (–)- $\alpha$ -ambrinol showed its animal, indol-, or skatol-like naphthalenic odour properties which seem to dominate the odour impression of



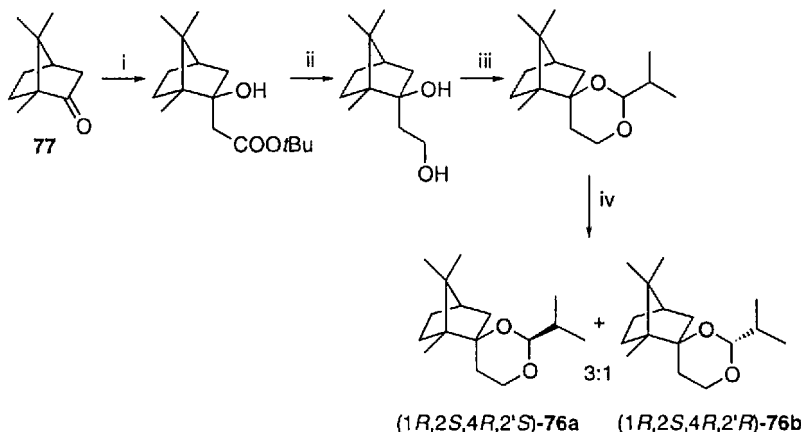
**Scheme 13.** Reagents and conditions: (i) (–)-camphanoylchloride, DMAP, CH<sub>2</sub>Cl<sub>2</sub>; then crystallisation from pentane–diethyl ether; (ii) LiAlH<sub>4</sub> in diethyl ether.

the racemate. The odour thresholds of the two enantiomers differed only by a factor of 1.5 to 2.

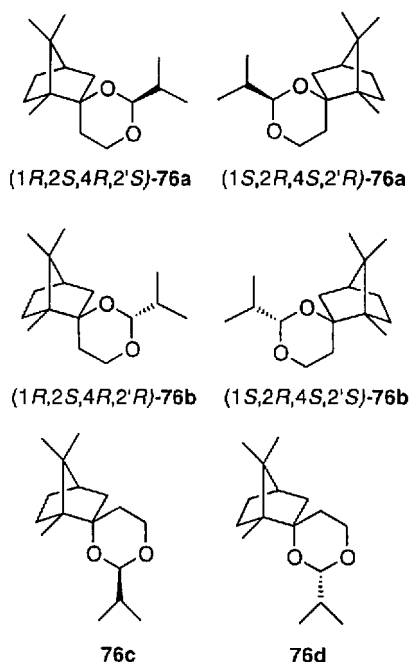
In 1987 Quest International discovered a new class of ambergris odorants, belonging to the 2-cyclohexenyl-1,3-dioxane family.<sup>69</sup> The most notable of these compounds was commercialised under the name of Karanal® 75. This latter was a mixture of eight pairs of enantiomers, of which only four were found to be organoleptically active, three of strong intensity and one weak. The absolute configuration of the active enantiomers was not determined. However, NMR spectroscopy and X-ray crystallography revealed that the active stereoisomers had *cis* configuration about the dioxane ring, with the cyclohexenyl ring equatorial, and the *sec*-butyl axial.<sup>34</sup>



Recently, Bajgrowicz et al. proposed a new camphor derived odorant, designed with the help of an amber olfactophore model.<sup>70</sup> As expected, the racemic mixture of 2'-isopropyl epimers 76a and 76b, that best fitted to the amber hypothesis, also possessed the most appreciated olfactory properties. Using the olfactophore model, it was difficult to discriminate between the four stereoisomers.

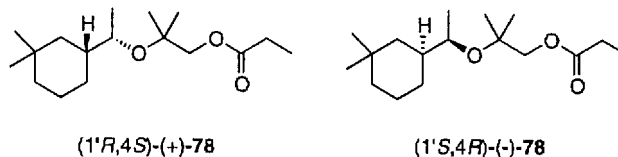


**Scheme 14.** Reagents and conditions: (i) *iso*-PrMgCl, AcO*tert*-Bu, –20°C; (ii) LiAlH<sub>4</sub>; (iii) Me<sub>2</sub>CHCHO, *p*-TsOH; (iv) flash chromatography, and crystallisation from EtOH/H<sub>2</sub>O.



Therefore, although the best mapping was observed for 76a, all four stereoisomers were prepared starting from (+)- and (–)-camphor 77, taking advantage of the stereoselective *endo*-addition of *t*-butyl acetate enolate to camphor (Scheme 14), followed by reduction and subsequent ketalisation. Single stereoisomers of 76a and 76b were isolated from each pair of diastereoisomers by flash chromatography and repeated crystallisations. All the four prepared stereoisomers of 76 presented some amber/woody aspects in their odour, but the scent of (1*R*,2*S*,4*R*,2'*S*)-76a resulted to be the strongest and the most amber-like. (1*R*,2*S*,4*R*,2'*S*)-76a was the isomer best fitting the model, and the one prepared starting from the natural (+)-camphor. As the final product still contained up to 2% of each of the other two epimers 76c and 76d, the synthesis of these two minor components was undertaken, according to Scheme 15, in order to evaluate their contribution to the odour profile of

76a. The results of the odour evaluation are reported in Table 4. These data confirmed the superiority of 76a, and established that the presence of traces of minor stereoisomers had no detrimental effect on the odour qualities of this one.



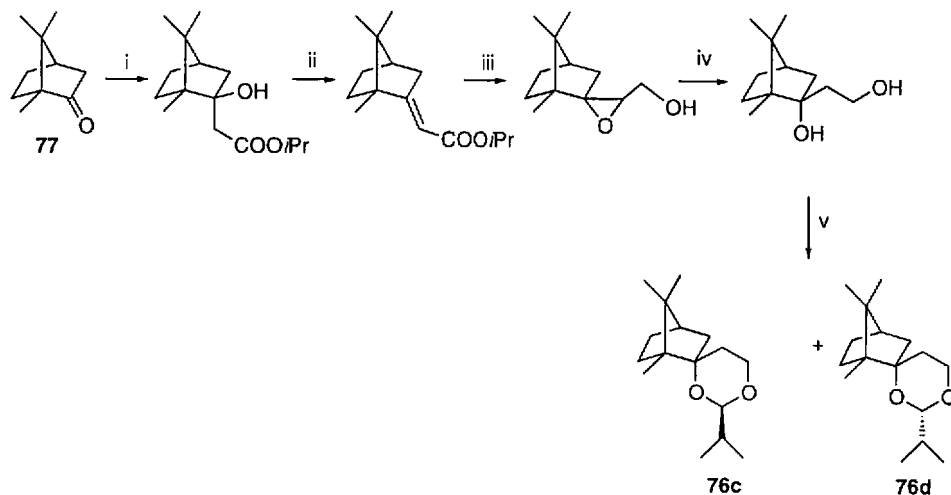
### 3. Musk odorants<sup>71</sup>

*“Lecteur, as-tu quelquefois respiré  
avec ivresse et lente gourmandise  
ce grain d’encens qui remplit une église,  
ou d’un sachet le musc invétéré?”*  
(C. Baudelaire, Les Fleurs du Mal, *Un fantôme*)

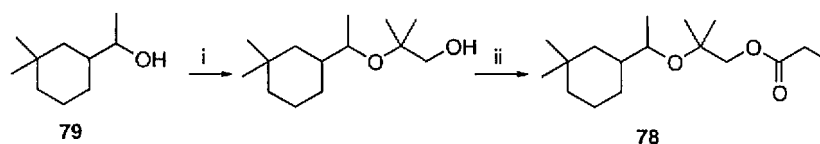
“O reader, have you ever breathed dust?  
With slow and drunken rapture have you craved  
The grain of incense filling up the nave,  
Or the sachet of inveterate musk?”  
(translated by William A. Sigler)

Table 4. Odour properties of derivatives 76a–d

Compound	Odour description	GC odour threshold (ng/l air)
(1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i> ,2' <i>S</i> )-76a	Amber, woody, cedarwood, animal, strong	0.2
(1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i> ,2' <i>R</i> )-76b	Woody, cedarwood, rosy, spicy, weak	40
(1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i> ,2' <i>R</i> )-76a	Woody, camphoraceous, amber, spicy, weak	88
(1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i> ,2' <i>S</i> )-76b	Woody, piney, slightly amber, weak	40
(1 <i>R</i> ,2 <i>R</i> ,4 <i>R</i> ,2' <i>R</i> )-76c	Camphoraceous, fruity, amber, woody, creamy	4
(1 <i>R</i> ,2 <i>R</i> ,4 <i>R</i> ,2' <i>S</i> )-76d	Woody, cedarwood, drier than 76c	250



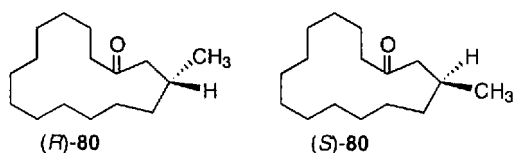
Scheme 15. Reagents and conditions: (i) *iso*-PrMgCl, *iso*-Pr<sub>2</sub>NH, AcO*iso*-Pr, –20°C; (ii) BF<sub>3</sub>Et<sub>2</sub>O; (iii) LiAlH<sub>4</sub>; MCPBA, NaHCO<sub>3</sub>; (iv) LiAlH<sub>4</sub>; (v) Me<sub>2</sub>CHCHO, *p*-TsOH.



Scheme 16. Reagents and conditions: (i) isobutylene oxide,  $\text{BF}_3\text{Et}_2\text{O}$ , cyclohexane; (ii) propionic anhydride.

Musk odorants play a key role in perfumery. Their characteristic odour is described as *warm, sensual, animal, natural*,<sup>72</sup> and they represent an essential part of the dry down of most perfume compositions. The typical musk odour is found in a large variety of very different structural types, such as the macrocyclic musks, the benzenoid musks, and a new third class of alicyclic compounds. The macrocyclic musk odorants<sup>73</sup> have become increasingly important for their good biodegradability. However, the benzenoid musks Tonalide® (Polak's Frutal Works; identical to Fixolide® (Givaudan)) 13, and Galaxolide® (International Flavours and Fragrances) 12 still represent the highest tonnage products, thanks to an optimal price/performance ratio, although they have shown some bio-accumulation problems. Helvetolide® (Firmenich) 78<sup>74</sup> is representative of a new third class of musk odorants. (+)- and (–)-Helvetolide were prepared, starting from (+)- and (–)-79 (Scheme 16). (+)-78 was described as *more intense and more musky than the (–)-enantiomer*, which was however found quite similar in tonality.

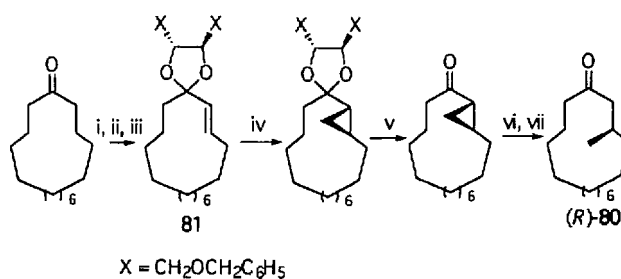
tridecanolide 82, which was found in the Angelica root oil (*Archangelica officinalis* Hoffm. syn. *Angelica archangelica* L.) in the ratio  $R/S=72/28$ .<sup>79</sup> The two enantiomers of macrolide 82 were prepared by Tochtermann and Kraft by a ring enlargement route, using the enantiopure chiral synthons (*R*)- and (*S*)-83, obtained via enzymatic methods (Scheme 18). The (*R*)-enantiomer was described to show a *clean, crystal-clear musk top note with strong, elegant woody accents. These are not cedarwood-like, but more directed towards a sandalwood tonality; a slight fruity undertone of pear is also present*.<sup>80</sup> The (*S*)-isomer has an *animalic musk tonality with camphoraceous aspects*.<sup>81</sup> The same tactics in ring enlargement was employed to prepare other macrocyclic musks which showed enantioselectivity in the odour receptor interaction: (i) the two enantiomers of one possible diastereoisomer of 12-methyl-13-tetradecanolide 84;<sup>82</sup> (ii) (+)- and (–)-muscolide 85;<sup>83</sup> (iii) the two enantiomers of an oxo derivative of muscolide 86.<sup>83</sup> The olfactory evaluations of these samples gave the following results.



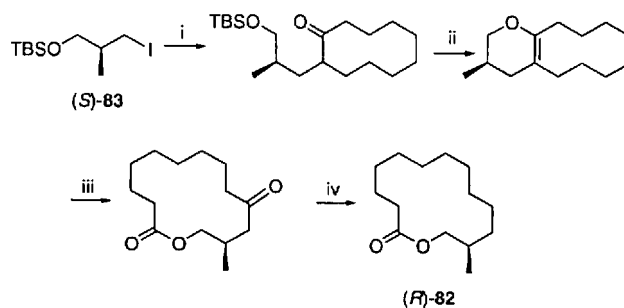
### 3.1. Macrocyclic musks

Muscone 80, the principal odorous component of the secretion of the male musk deer *Moschus moschiferus*, was discovered in 1906.<sup>75</sup> Its structure<sup>76</sup> and absolute<sup>77</sup> configuration were determined later to be (*R*)-3-methylcyclopentadecanone. In 1989, Pickenhagen<sup>31c</sup> prepared (*R*)-(–)-muscone (ee=95.5%) and (*S*)-(+)-muscone (ee=97.7%) for olfactory evaluation, following the enantioselective synthesis of Nelson and Mash<sup>78</sup> (Scheme 17). The key step was the diastereoselective cyclopropanation of homochiral ketal 81. The musk note of natural (*R*)-80 was described as *very nice musky note, rich, and powerful*, that of the (*S*)-enantiomer was found *poor, and less strong*. Thresholds measured in water, using Guadagni's procedure, were 61 and 233 ppb, respectively. From these results, the author could deduce that the methyl group of (*S*)-80 somehow hindered easy access of the molecule to its receptor. His hypothesis was supported by the fact that 3,3-dimethylcyclopentadecanone was nearly odourless.

Another interesting compound belonging to the class of macrocyclic musk odorants and showing different odour qualities between enantiomers is 12-methyl-13-



Scheme 17. Reagents and conditions: (i)  $\text{Br}_2$ , MeOH; (ii) 1,4-di-*O*-benzyl-D-threitol, *p*-TsOH, benzene; (iii) MeONa, DMSO; (iv) Zn–Cu,  $\text{CH}_2\text{I}_2$ , ether; (v) 10% HCl, MeOH; (vi) Li, *t*-BuOH,  $\text{NH}_3$  (l), ether; (vii) pyridinium dichromate,  $\text{CH}_2\text{Cl}_2$ .



Scheme 18. Reagents and conditions: (i) LDA, HMPA, cyclodecanone, THF; (ii) Amberlyst 15; (iii)  $\text{O}_3$ , MeOH; (iv)  $(\text{H}_2\text{N})_2\text{CS}$ ; (v)  $\text{NH}_2\text{NHTs}$ , MeOH; (vi)  $(\text{PPh}_3)_2\text{CuBH}_4$ ,  $\text{CHCl}_3$ .

Instead of musk odour, (12*S*,13*R*)-(-)-**84** possessed an animalic cedarwood odour with camphoraceous aspects. (12*R*,13*S*)-(+)-**84** showed a strong woody note, with relatively pronounced musk note.

The odour of (*R*)-muscolide, related to naturally occurring (*R*)-muscone was slightly erogenous, animalic, resembling that of natural musk tincture. (*S*)-Muscolide was of weak intensity, but possessed a very pleasant musk note with a more distinctive erogenous-animalic character. This parallels the case of 12-methyl-13-tridecanolides **82**, where the (*S*)-enantiomer has animalic facets while the (*R*)-enantiomer has not. As for the oxo derivative of muscolide, (*R*)-**86** smelled slightly musky and sweet, but not erogenous-animalic. (*S*)-**86** also possessed a weak musk note, without animalic character, and, in contrast to the (*R*)-enantiomer, was dominated by an odour reminiscent of ironed linen.

In search of new macrocyclic musk lactones, in 1998 Kraft and Cadalbert prepared various 4-substituted 1,7-dioxacycloalkan-8-ones.<sup>84</sup> They found that the most powerful musk odorant was 12-methyl-9-oxa-14-tetradecanolide **87**. Its odour was described to be musky, floral, woody, myrrh, fresh, powdery, reminiscent of musk ambrette. They were able to verify by chiral GC olfactometry that one enantiomer was odourless, and therefore decided to establish the absolute configuration of the enantiomer responsible for the odour by stereoselective synthesis. The stereoselective step was the enantioselective monoesterification of prochiral 3-methylglutaric anhydride with (*S*)-1-(1'-naphthyl)-ethanol, to afford derivative **88** (Scheme 19). (*R*)-**87** (ee=87.2%) was obtained, and showed the same odour qualities of the racemate, though more intense.

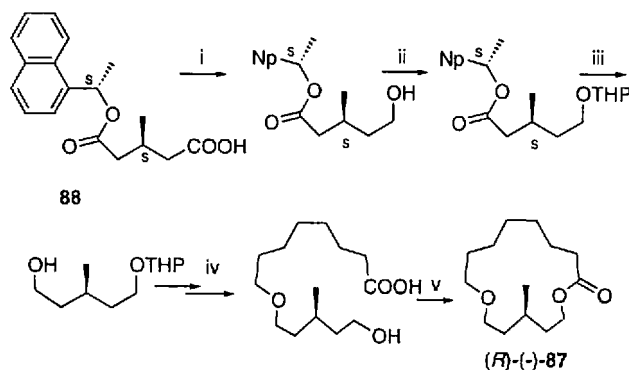
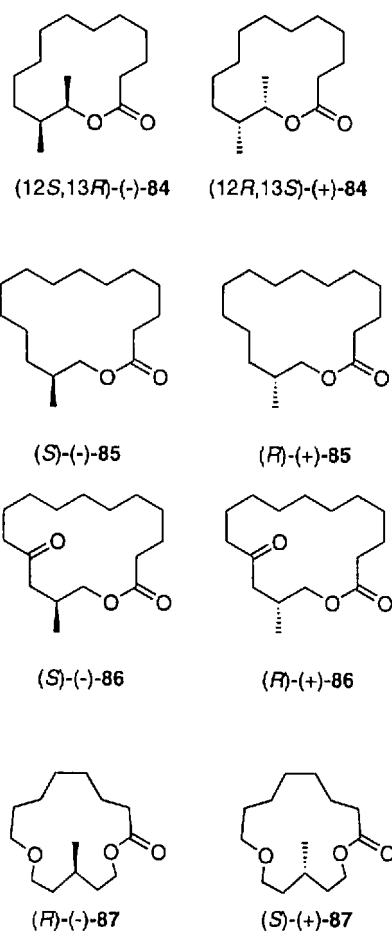
In 1999 Nirvanolide® (Givaudan) **89** was prepared<sup>85</sup> from non-racemic precursor **90** (Scheme 20). The (*S*) enantiomer of Nirvanolide was found odourless by chiral GC olfactometry, and the (*R*)-enantiomer resulted to be musky, fruity, powdery with lactonic nuances.

### 3.2. Benzenoid musks

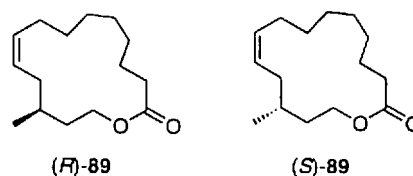
The first synthetic musks were highly substituted nitroarenes, such as musk ketone **91**, obtained by chance by Baur<sup>86</sup> while he was working at the preparation of new explosives. The nitro musks have been widely used in perfumery for several years. Their usage began to decrease in the eighties, because of their photochemical reactivity leading to discoloration, and skin sensitisation problems. The evolution of benzenoid musks led to the more stable compound Phantolide® **92**, the first commercial nitro-free aromatic musk.<sup>87</sup>

Some interesting data on the enantioselectivity of the odour sensation of nitro free benzenoid musk odorants have been reported in the literature.

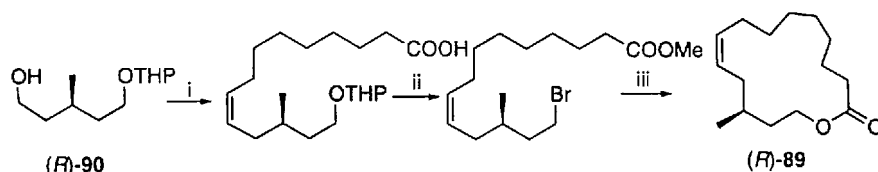
Tonalide® (= Fixolide®) (**13**). The enantioselective synthesis of (*S*)-(-)- and (*R*)-(+)-Tonalide was based on the Friedel–Crafts acylation of toluene with (*S*)- and



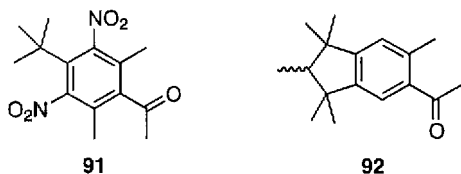
**Scheme 19.** Reagents and conditions: (i)  $\text{BH}_3\text{SMe}_2$ , THF,  $0^\circ\text{C}$ ; (ii) dihydropyran,  $\text{CH}_2\text{Cl}_2$ , PPTS; (iii)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ ; (iv)  $\text{NaH}$ , 1,4-dioxane, 1-(7'-bromoheptyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane;  $\text{HCl}$ , 2*N*,  $\text{AcOEt}$ ;  $\text{KOH}$ ,  $\text{EtOH}$ ; (v)  $\text{KOH}$ , 20–23 mbar,  $50\%$ ,  $195^\circ\text{C}$ ;  $\text{MeOK}$ , glycerol,  $155^\circ\text{C}$ , 4–6 mbar.



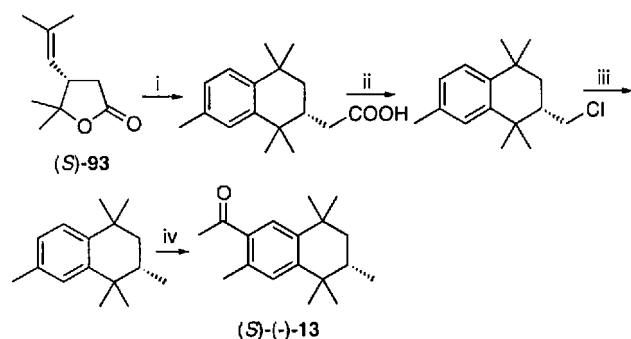




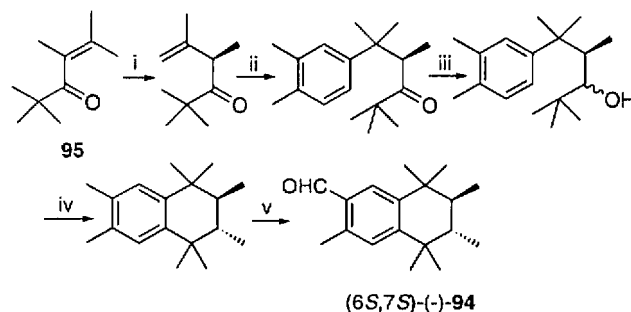
Scheme 20. Reagents and conditions: (i) PCC,  $\text{CH}_2\text{Cl}_2$ ;  $\text{Br}^-\text{Ph}_3\text{P}^+(\text{CH}_2)_7\text{COOH}$ ,  $t\text{-BuOK}$ ; (ii) MeOH,  $p\text{-TsOH}$ ;  $\text{CBr}_4$ ,  $\text{Ph}_3\text{P}$ ,  $\text{CH}_2\text{Cl}_2$ ; (iii) NMP, KOH, MeOH,  $\text{H}_2\text{O}$ ;  $\text{K}_2\text{CO}_3$ .



(*R*)-pyrocine **93**, respectively (Scheme 21). The (*S*)-(-)-enantiomer of Tonalide<sup>®</sup> showed a *strong musk odour with a good fixation property*,<sup>88</sup> whereas the (*R*)-enantiomer showed a *light and sweet aromatic odour*. A constitutional isomer of Tonalide<sup>®</sup>, aldehyde **94**, was prepared by Fehr et al.<sup>89</sup> The two enantiomers were obtained by enantioselective protonation of the lithium enolate of ketone **95**, by using (-)- and (+)-*N*-isopropylphedrine as chiral catalysts (Scheme 22). (6*S*,7*S*)-(-)-**94** (ee = 77%) was described as *musky, very earthy, slightly ambery, and with a very strong odour*, whereas (+)-(6*R*,7*R*)-**94** (ee = 82%) was found *less earthy, less odorous, with an additional woody tonality*.

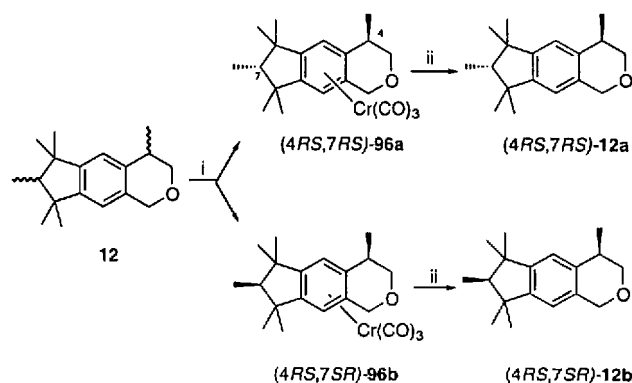


Scheme 21. Reagents and conditions: (i) toluene,  $\text{AlCl}_3$ ; (ii)  $\text{Pb}(\text{OAc})_4$ ,  $\text{LiCl}$ ; (iii)  $\text{LiAlH}_4$ , THF; (iv)  $\text{AcCl}$ ,  $\text{AlCl}_3$ , 1,2-dichloroethane.



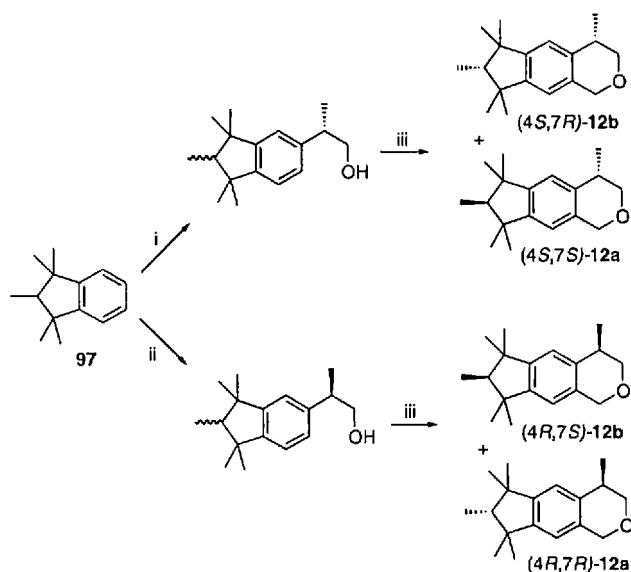
Scheme 22. Reagents and conditions: (i) LDA, THF; (-)-*N*-isopropylphedrine; (ii) *o*-xylene,  $\text{AlCl}_3$ ; (iii)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ ; (iv)  $\text{H}_2\text{SO}_4$ ,  $\text{CH}_2\text{Cl}_2$ ; (v)  $\text{Ce}(\text{NH}_4)_2(\text{NO}_3)_6$ , MeOH.

Galaxolide<sup>®</sup> **12**. The olfactory characterisation of the enantiomerically pure isomers of Galaxolide<sup>®</sup> was reported by Frater et al. in 1999.<sup>90</sup> The authors started their investigation with the separation of the two diastereoisomers (4*RS*,7*RS*)-**12a** and (4*RS*,7*SR*)-**12b** via the corresponding tricarbonyl-( $\eta^6$ -cyclopenta[*g*]-2-benzopyran)chromium complexes **96a** and **96b** (Scheme 23). Chiral GC olfactometry of the two diastereoisomerically pure samples of (4*RS*,7*RS*)-**12a** and (4*RS*,7*SR*)-**12b** revealed that the configuration of one stereogenic carbon atom, and not the relative configuration of the methyl groups, was important in determining the odour properties of the compound. One enantiomer of the *cis*-diastereoisomer (4*RS*,7*SR*)-**12b** and one of the *trans*-diastereoisomer (4*RS*,7*RS*)-**12a** were found to have the typical musk odour. The enantioselective synthesis of all the four stereoisomers was thus carried out. By Friedel–Crafts reaction of (*S*)-methyloxirane with pentamethylindane **97** a 1:1 mixture of the two enantiomerically pure (4*S*,7*R*)-**12b** and (4*S*,7*S*)-**12a** was obtained (Scheme 24). The two diastereoisomers were then separated according to the procedure optimised for the racemic materials. By using (*R*)-methyloxirane, (4*R*,7*S*)-**12b** and (4*R*,7*R*)-**12a** were prepared. (4*S*,7*R*)-(-)-**12b** was found to be the most powerful (odour threshold = 0.63 ng/l air) of the Galaxolide<sup>®</sup> isomers, and to possess a *very pleasant clean musk note*. Slightly less powerful was the *trans*-diastereoisomer (4*S*,7*S*)-**12a** (odour threshold = 1.0 ng/l air) which showed a *similar musk odour that differed from that of (4*S*,7*R*)-**12b** by its dry character*.



Scheme 23. Reagents and conditions: (i)  $\text{Cr}(\text{CO})_6$ ,  $\text{Bu}_2\text{O}$ , THF; (ii)  $\text{H}_2\text{SO}_4$ ,  $h\nu$ , benzene, acetonitrile.

The (4*R*)-isomers were found to be much weaker, and to give no contribute to the odour profile of the commercial product. Isomer (4*R*,7*S*)-**12b** (odour threshold = 130 ng/l air) was still a bit musk. (4*R*,7*R*)-**12a** (odour threshold = 440 ng/l air) was very weak, showing an odour which was mainly fruity. Some perfumers judged (4*R*,7*R*)-**12a** odourless.



**Scheme 24.** Reagents and conditions: (i) (*S*)-methyloxirane; (ii) (*R*)-methyloxirane; (iii)  $(\text{CH}_2\text{O})_x$ ,  $\text{H}_2\text{SO}_4$  cat.

**Vulcanolide<sup>®</sup> (98).** In 1989 Fehr et al.<sup>72</sup> reported that the introduction of supplementary methyl groups into the basic structure of benzenoid musks lead to excellent new musk odorants, showing 'densely packed structures of enhanced lipophilicity but of similar global shape'. This led to the preparation of **Vulcanolide<sup>®</sup>**, which was found to be 10–20 times stronger than Tonalide<sup>®</sup>, previously considered as the strongest musk odorant. The

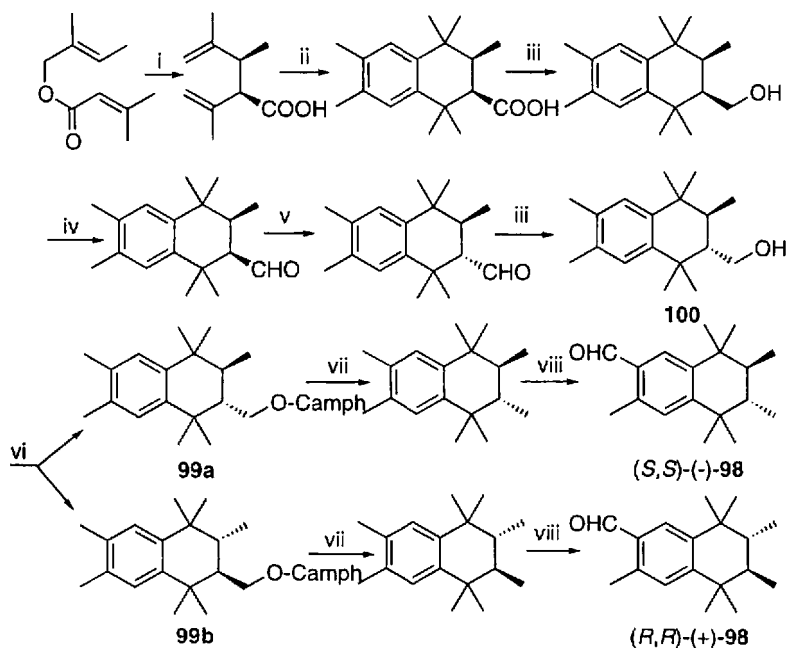
enantiomers of Vulcanolide have been recently prepared.<sup>91</sup> The key step was the separation of the camphanic esters **99a** and **99b** of the racemic alcohol intermediate **100** by column chromatography (Scheme 25). (*S,S*)-(-)-Vulcanolide<sup>®</sup> (ee=98%) was found to be extremely strong, both on the smelling strip and in perfume compositions. An earthy note predominated on the smelling strip, but only the musk character was perceived in perfume compositions or by smelling the crystals. (*R,R*)-(+)-Vulcanolide (ee=98%) was much weaker and less tenacious, still showing an agreeable musk odour. It can not be excluded that the odour of (+)-**98** is due to trace amounts of (-)-**98**. In the same work the *cis* diastereoisomer of Vulcanolide<sup>®</sup> was synthesised and found almost odourless. An enantioselective route to the most valuable (-)-**98** has been recently optimised,<sup>92</sup> based on enantioselective protonation.

#### 4. Floral odorants

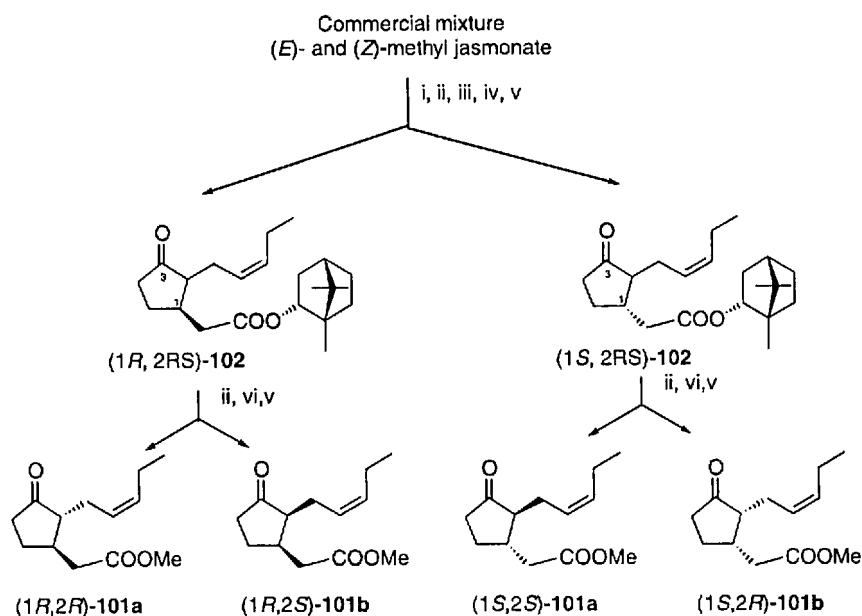
"The forward violet thus did I chide:  
sweet thief, whence didst thou steal thy sweet that smells,  
if not from my love's breath?"  
(W. Shakespeare, Sonnets, no. 99)

##### 4.1. Jasmonates and dihydrojasmonates

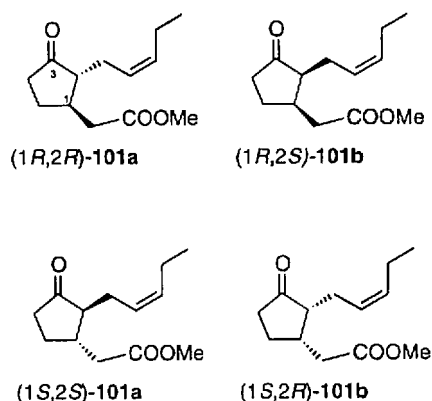
(1*R*,2*R*)-(-)-Methyl (*Z*)-jasmonate (1*R*,2*R*)-**101a** and its diastereoisomer (+)-(1*R*,2*S*)-**101b** occur in nature in the proportions of 97:3 as the odorous principle of jasmin flower oil (*Jasminum grandiflorum* L.)<sup>93</sup>, whereas their enantiomers are nearly odourless.



**Scheme 25.** Reagents and conditions: (i) LDA,  $\text{Me}_3\text{SiCl}$ ; (ii)  $\text{AlCl}_3$ , *o*-xylene; (iii)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ ; (iv) PCC,  $\text{CH}_2\text{Cl}_2$ ; (v) *t*-BuOK, *t*-BuOH; (vi) (-)-camphanoyl chloride, pyridine, DMAP; then column chromatography; (vii) KOH, EtOH; *p*-TsCl, pyridine;  $\text{LiBHET}_3$ , THF; (viii)  $\text{Ce}(\text{NH}_4)_2(\text{NO}_3)_6$ , MeOH.



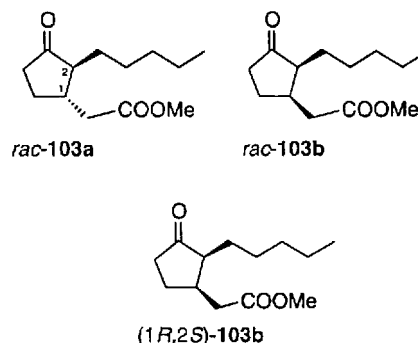
**Scheme 26.** Reagents and conditions: (i) column chromatography ( $\text{AgNO}_3$ ); (ii) KOH, EtOH; (iii)  $\text{SOCl}_2$ , pyridine; (iv) (–)-borneol, benzene; (v) HPLC; (vi)  $\text{CH}_2\text{N}_2$ ,  $\text{Et}_2\text{O}$ .



The odour thresholds of all stereoisomers of methyl jasmonate were reported by Acree et al. in 1985.<sup>19</sup> The starting material for the preparation of all the stereoisomers of compound **101** was commercial methyl jasmonate, a racemic mixture of four (*E*)-isomers and of four (*Z*)-isomers (Scheme 26). Column chromatography with 15%  $\text{AgNO}_3$  on silica allowed the recovery of (*Z*)-isomers. These latter derivatives were hydrolysed and converted into the corresponding bornyl esters by reaction of the acyl chloride with (–)-borneol. The two mixtures of enantiopure bornyl ester diastereoisomers, i.e. (1*S*,2*RS*)-**102** and (1*R*,2*RS*)-**102**, were separated by HPLC. Hydrolysis and reaction with diazomethane gave two mixtures, one containing (1*R*,2*R*)-**101a** and (1*R*,2*S*)-**101b**, and the other containing (1*S*,2*S*)-**101a** and (1*S*,2*R*)-**101b**. The two diastereoisomers of each pair were separated by HPLC (Scheme 26).<sup>94</sup> Stereoisomers (1*S*,2*S*)-**101a** and (1*S*,2*R*)-**101b** were found odourless, while their corresponding enantiomers (1*R*,2*R*)-**101a** and (1*R*,2*S*)-**101b** possess a typical floral, jasmine, slightly fruity odour. The following values of odour threshold were determined in ethanol solution, according to the triangular test procedure:

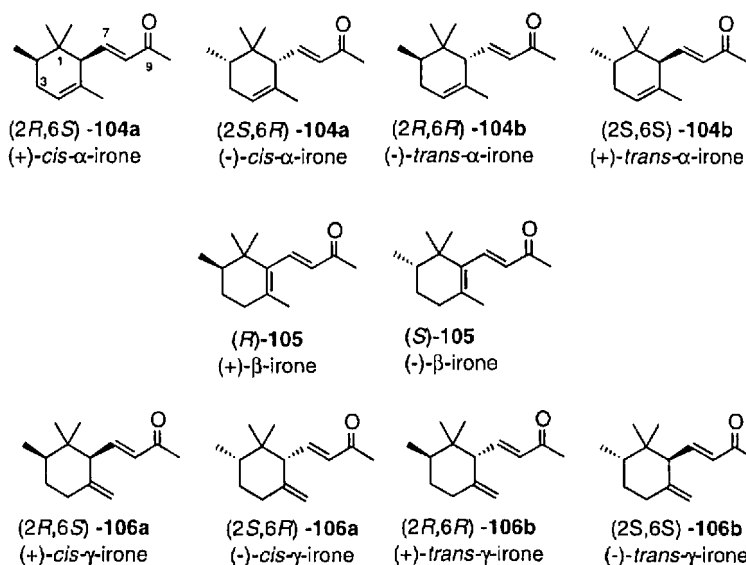
commercial mixture 90 ng/ml; (±)-**101a** 5700 ng/ml; (±)-**101b** 13 ng/ml; (1*R*,2*R*)-**101a** >70 ng/mL, (1*R*,2*S*)-**101b** 3 ng/ml.

Dihydro derivative **103**, which was prepared in the course of the structure elucidation of natural **101a**, was found to have very interesting odour properties. It soon became widely employed in perfumery, with the commercial name of Hedione®. Commercial Hedione® contains 90% of *rac*-**103a** and 10% of the much more powerful diastereoisomer *rac*-**103b**. Several attempts have been made to increase the content of the olfactory active racemic *cis*-diastereoisomer in order to optimise the performance of the commercial product.<sup>95</sup> The odour of **103b** is mainly due to (1*R*,2*S*)-**103b**, while the other enantiomer is very weak, and more earthy than floral.<sup>32b,95b</sup>



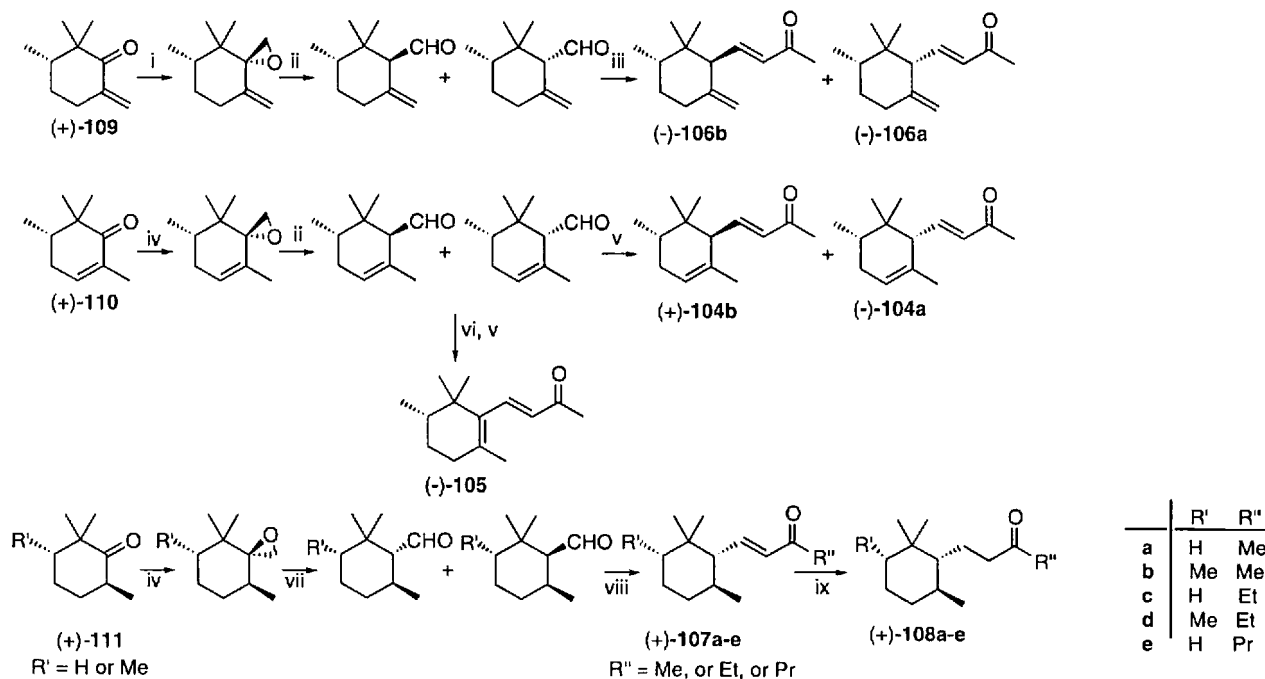
#### 4.2. Irones

Irones **104–106** are the odoriferous principle of natural *Orris* root oil. They were first isolated from *Iris* rhizome in 1893.<sup>96</sup> Their correct molecular formula was established 40 years later,<sup>97</sup> their structure defined, independently, by Ruzicka<sup>98</sup> and Naves,<sup>99</sup> and the absolute configuration



determined by Rautentstrauch and Ohloff.<sup>100a</sup> It has been established that the distribution of irone isomers and enantiomers in different qualities of iris oils depends upon the botanical species of the plant.<sup>100</sup> The average composition<sup>101</sup> of an iris butter prepared from *Iris germanica* is the following: 0.91% of (+)-*trans*-α-irone ee = 96%, (+)-**104b**, 61.48% of (-)-*cis*-α-irone ee = 82%, (-)-**104a**, 0.71% of β-irone **105** and 37.60% of (-)-*cis*-γ-irone ee = 38%, (-)-**106a**. When *Iris pallida* rhizomes are used, the corresponding iris butter contains 4.16% of (+)-*trans*-α-irone ee = 98%, (+)-**104b**, 34.46% of (+)-*cis*-α-irone ee = 66%, (+)-**104a**, 0.16% of β-irone **105** and 61.26% of (+)-*cis*-γ-irone ee = 96%, (+)-**106a**.

In 1993 Chapuis and Brauchli<sup>102</sup> prepared optically active irones (+)- and (-)-**104a**, (+)- and (-)-**104b**, (+)- and (-)-**105**, (+)- and (-)-**106a**, (+)- and (-)-**106b**, and the analogues **107a–e** and **108a–e**, exploiting as a key step the Corey–Chaykovsky oxiranylation of both the enantiomers of ketones **109**, **110**, and **111** (R' = H, R' = CH<sub>3</sub>), according to Scheme 27. Enantiopure α- and γ-irone diastereoisomers were separated by preparative GC. Derivatives **107a–e** and **108a–e** were obtained as single enantiopure diastereoisomers. The following sensory evaluations were reported; (i) (-)-*trans*-γ-**106b** (ee = 76%) typically irone, green scent; (ii) (+)-*trans*-γ-**106b** (ee = 80%) irone, rooty odour; (-)-*cis*-γ-**106a** (ee =

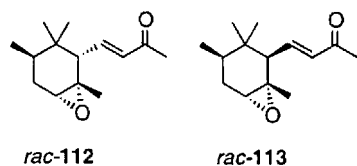


**Scheme 27.** Reagents and conditions: (i) Me<sub>3</sub>Si, DMSO, NaOH; (ii) SnCl<sub>4</sub>, toluene; (iii) Ph<sub>3</sub>P=CHCOMe, toluene; (iv) Me<sub>2</sub>S, Me<sub>2</sub>SO<sub>4</sub>, DMSO, NaOH; (v) acetone, EtONa, EtOH; (vi) EtONa, EtOH; (vii) MgBr<sub>2</sub>, toluene; (viii) R'COMe, EtONa, EtOH; (ix) H<sub>2</sub>, 5% Pd/C, AcOEt.

76%) irone, violet; (+)-*cis*- $\gamma$ -106a Orris, rooty. The sensory descriptions of derivatives 107a–e and 108a–e are reported in Table 5: ketones (+)-107a–e were olfactively superior to their enantiomers due to their organoleptic properties and strength.

In the aim of understanding the odour difference of *Orris* oils of different origins, experiments were carried out in 1993 by Petrzilka et al.<sup>101</sup> based on the direct enantioselective separation and olfactory evaluation of irone isomers. Racemic irone isomers were resolved by chiral capillary gas chromatography and the odour properties of the separated pure enantiomers were characterised by using GC-sniffing techniques (Table 6). (+)-*cis*- $\alpha$ -irone and (+)-*cis*- $\gamma$ -irone were found to show the most interesting organoleptic properties. In the last 4 years we have developed chemo-enzymatic approaches to the preparation of the ten irone isomers.<sup>103</sup>

By treatment of *Irone alpha*® (a commercial mixture of ( $\pm$ )-104a and ( $\pm$ )-104b 45:55 with 5% of 105) with *m*-chloroperbenzoic acid in methylene chloride we obtained the two epoxides 112 and 113, which were separated by column chromatography, thus allowing us to separate *cis*- $\alpha$ - and *trans*- $\alpha$ -irone derivatives. Racemic epoxy- $\alpha$ -irols 114 and 115, obtained upon NaBH<sub>4</sub> reduction of 112 and 113, respectively, and brought to diastereoisomeric purity by column chromatography, were submitted to enzyme-mediated kinetic resolution (Scheme 28). The enantiopure alcohol and acetate derivatives obtained were converted into epoxy ketones, and deoxygenated to afford (–) and (+)-104a and (–) and (+)-104b.<sup>103a</sup>



Compounds (+)- and (–)-116 and (+)- and (–)-117 were intermediates in the preparation of *cis*- and *trans*- $\gamma$ -irones (Scheme 29). They were submitted to photoisomerisation in isopropanol, using xylene (10%) as photosensitiser, to give after 12 days and 27 h, respectively, enantiopure *trans*- and *cis*- $\gamma$ -irol acetates. After saponification and MnO<sub>2</sub> oxidation, (–) and (+)-106b and (+)- and (–)-106a were obtained.<sup>103c</sup>

We prepared (+)- and (–)-*trans*- $\gamma$ -irone even from the racemate (Scheme 30). The two racemic alcohol diastereoisomers 118a and 118b, obtained upon NaBH<sub>4</sub> reduction of 106b, were separated by fractional crystallisation of the corresponding 4-nitrobenzoate esters from hexane.  $\gamma$ -Irol 118a was then recovered as a pure diastereoisomer and resolved by transesterification with Lipase PS. Enantiopure acetate and alcohol were then easily converted into (+)- and (–)-*trans*- $\gamma$ -irone.<sup>103c</sup>

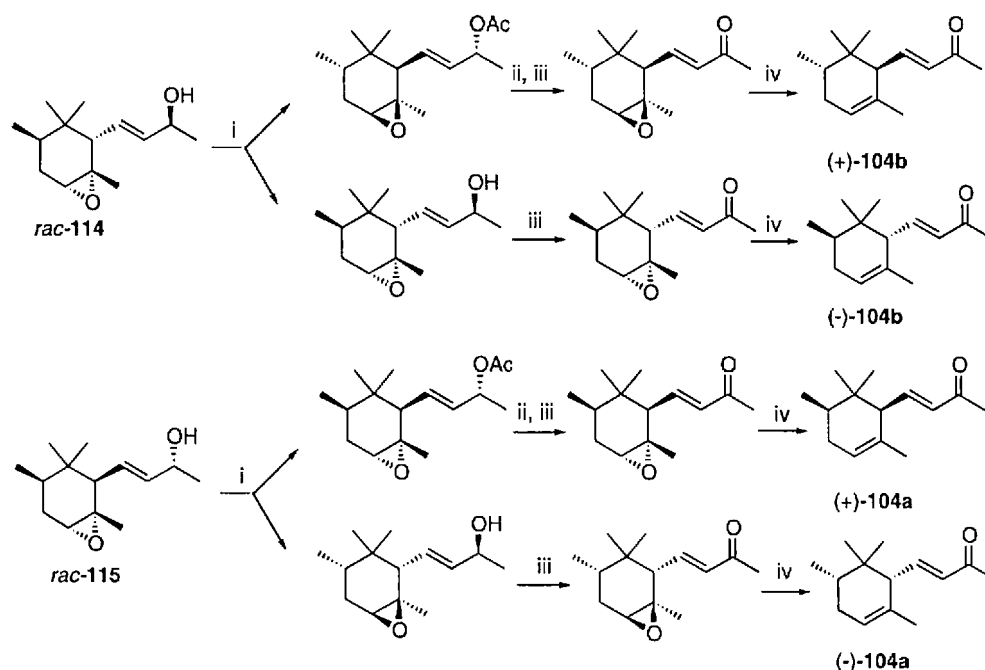
**Table 5.** Odour properties of compounds 107a–e and 108a–e

Compound	Odour description
(–)-107a	Woody, ionone, leather, camphor, weak
(+)-107a	Aromatic, carvone, woody, humus, powdery, ionone, myrrh, violet, strong
( $\pm$ )-107a	Woody, ionone
(–)-107b	Woody, powdery, incense
(+)-107b	Nicely Orris, irone, balsamic, myrrh
( $\pm$ )-107b	Orris, powdery, violet, myrrh
(–)-107c	Saffron, woody, floral
(+)-107c	Oily
( $\pm$ )-107c	Floral, fruity, methylionone
(–)-107d	Woody
(+)-107d	Woody, Orris, powdery, myrrh, balsamic
( $\pm$ )-107d	Mouldy, humus, earthy
(–)-107e	Woody, dry
(+)-107e	Liquor, quince, violet, woody, powdery
( $\pm$ )-107e	Woody, vague
(–)-108a	Woody, cedar, powdery
(+)-108a	Woody, powdery, amber, ionone
( $\pm$ )-108a	Woody
(–)-108b	Unpleasant
(+)-108b	Woody, powdery, ambergris
( $\pm$ )-108b	Woody, amber, myrrh, pleasant
(–)-108c	Amber, woody, saffron
(+)-108c	Woody, irone, weak
( $\pm$ )-108c	Woody
(–)-108d	Woody
(+)-108d	Woody, weak, irone
( $\pm$ )-108d	Woody, weak, vague
(–)-108e	Ionone, woody
(+)-108e	Myroxyde, lavender, woody, ionone
( $\pm$ )-108e	Vaguely woody, camphor

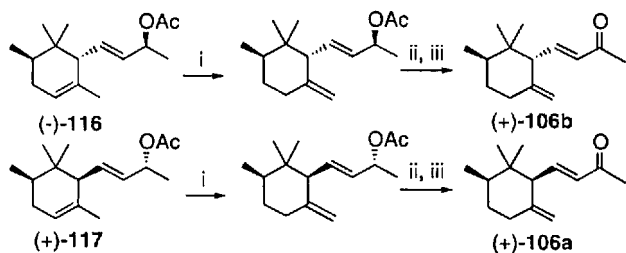
**Table 6.** Odour properties of irone samples according to Ref. 101

Compound	Odour description
(+)-104a	Iris, sweet irone odour, woody ionone, floral, fruity
(–)-104a	Odourless
(+)-104b	Floral, fresh, and fruity, irone and ionone type, honey, sweet, camomile effect, violet odour is weak
(–)-104b	Iris, sweet irone character, dry odour
(+)-105	Iris family, anis, liquorice, green
(–)-105	Poor, weakly iris
(+)-106a	Iris, sweet, woody ionone, dry floral
(–)-106a	Odourless
(+)-106b	Weak, burnt smell, metallic, chemical
(–)-106b	Iris, floral note, ionone, like <i>trans</i> - $\alpha$ -irone

LiAlH<sub>4</sub> reduction of epoxy-*cis*- $\alpha$ -irone 113 gave diol derivatives 119 and 120 which were separated by column chromatography and submitted to Lipase PS-mediated acetylation (Scheme 31). Dehydration of enantiopure acetates with POCl<sub>3</sub> and pyridine, followed by photoisomerisation, hydrolysis and oxidation, afforded (+)- and (–)-*cis*- $\gamma$ -irone 106a. Enantiopure alcohols were oxidised and then dehydrated, to afford (–) and (+)-106a.<sup>103b</sup>



**Scheme 28.** Reagents and conditions: (i) Lipase PS, *t*-butylmethyl ether, vinyl acetate; (ii) KOH in MeOH; (iii) MnO<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub>; (iv) NaI, (CH<sub>3</sub>)<sub>3</sub>SiCl, CH<sub>3</sub>CN.



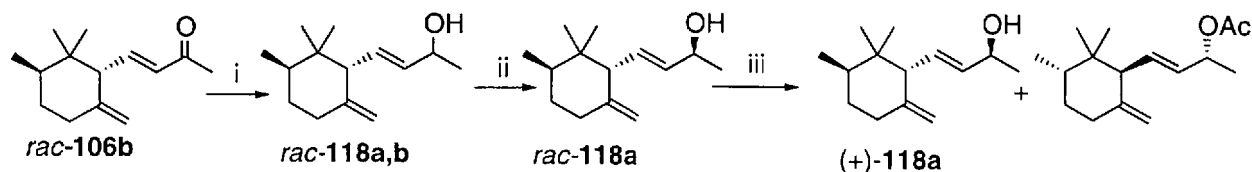
**Scheme 29.** Reagents and conditions: (i) *hν*, isopropanol, 10% xylene; (ii) KOH, MeOH; (iii) MnO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>.

Reductive ring opening of epoxy-*trans*- $\alpha$ -irone **112** gave diols **121** and **122**, which were separated and acetylated with Lipase PS to provide enantiomerically pure alcohol and acetate, and converted into  $\beta$ -irol acetates (–) and (+)-**123**, and (–) and (+)-**124** (Scheme 32), and then into (+) and (–)- $\beta$ -irone samples by hydrolysis and MnO<sub>2</sub> oxidation.<sup>103b</sup>

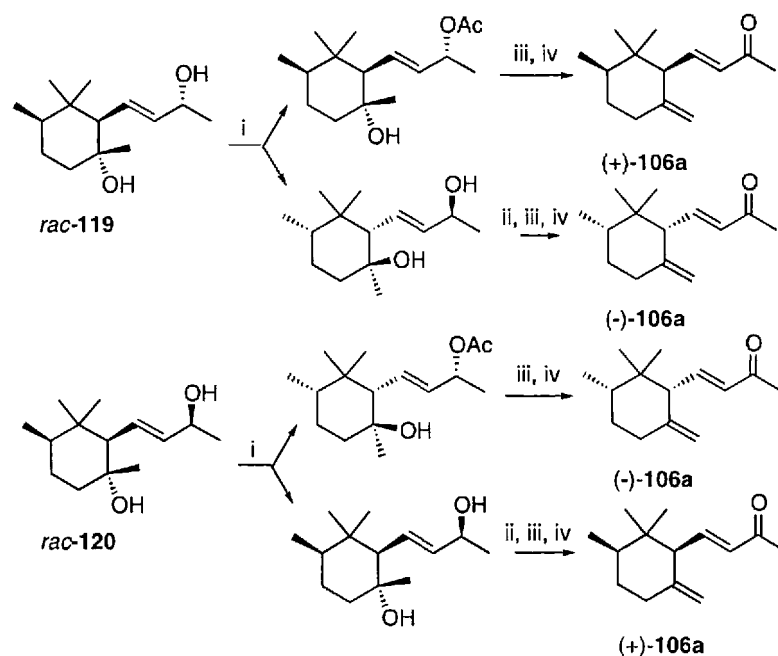
Thus, we had in hand samples of enantiopure irones to submit to olfactory evaluation. The results of this study are collected in Table 7, and are quite different from those obtained by Petrzilska by GC-sniffing. We found that (–)-*cis*- $\alpha$ -irone and (–)-*trans*- $\gamma$ -irone showed the delicate *Orris* butter character. This latter evaluation on isolated samples completed the knowledge of the olfactory properties of irone isomers. This investigation allowed to establish how the odour response of these compounds is sensible to the relative and absolute configuration at the two stereocentres at C<sub>2</sub> and C<sub>6</sub>.

### 4.3. Ionones

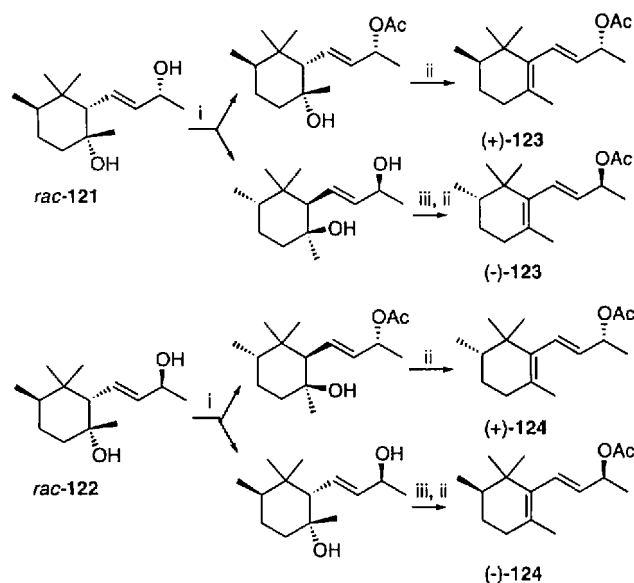
$\alpha$ -Ionone **125** is a precious fragrant ingredient for perfume compositions.<sup>104</sup> It became accessible on a large scale by chemical synthesis from citral in 1898.<sup>105</sup> In 1972 Uhde and Ohloff were able to show that ionones are the odoriferous principle of violets, being found in violet flower oil 8.22% of (*R*)- $\alpha$ -ionone (**125**) and 0.22% of  $\beta$ -ionone (**126**).<sup>106</sup>



**Scheme 30.** Reagents and conditions: (i) NaBH<sub>4</sub> in MeOH–CH<sub>2</sub>Cl<sub>2</sub>; (ii) 4-nitrobenzoyl chloride, pyridine; crystallisation from hexane; KOH in MeOH; (iii) Lipase PS, *t*-butylmethyl ether, vinyl acetate.



**Scheme 31.** Reagents and conditions: (i) Lipase PS, *t*-butylmethyl ether, vinyl acetate; (ii) Ac<sub>2</sub>O, pyridine; (iii) POCl<sub>3</sub> in pyridine; (iv) KOH in MeOH; then MnO<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub>.



**Scheme 32.** Reagents and conditions: (i) Lipase PS, *t*-butylmethyl ether, vinyl acetate; (ii) POCl<sub>3</sub> in pyridine; (iii) Ac<sub>2</sub>O in pyridine.

$\alpha$ -Ionone enantiomers were differently evaluated by different perfumers.

When Sobotka<sup>107</sup> first prepared (+)- and (-)- $\alpha$ -ionone he noticed 'a distinct difference in odour between the *d*- and *l*-form'. In 1947, Naves<sup>108</sup> submitted his samples of

(+)- and (-)-**125** to an olfactory evaluation by skilled perfumers. Both antipodes of  $\alpha$ -ionone were found to possess the same odour of racemic ionone, though less intense. As a matter of fact, the (*R*)- and (*S*)-enantiomers showed the same odour threshold (2–8 ng/l of air), but a lower threshold value was found for ( $\pm$ )-**125** (0.25–0.5 ng/l of air).

In 1989, Polak<sup>22</sup> measured the human odour response to  $\alpha$ -ionone enantiomers. Surprisingly, he found that the relative sensitivities to (+)- and (-)-**125** diverged widely, some subjects being much more sensitive to (+)- $\alpha$ -ionone than to (-)- $\alpha$ -ionone, and vice versa. In 63 subjects the (+)/(-) threshold concentration ratio varied over four orders of magnitude. Nine subjects with extreme values of (+)/(-)-ratio were further tested several times over seven months, and retained stable ratios. The same nine subjects were tested for threshold sensitivity to carvone enantiomers, and showed (+)/(-) ratios variable only in a narrow range. Thus, Polak suggested that the odour discrimination of  $\alpha$ -ionone enantiomers involves at least two receptors with different enantioselectivity, and that their distribution could vary independently in the human population. This result is in agreement with the data recently published by Rubin and Katz<sup>23b</sup> (see Section 1).

Researchers of Haarmann & Reimer<sup>109</sup> reported in 1991 a violet-like, fruity, raspberry-type, floral odour with a threshold of 0.5–5 ppb for (*R*)-(+)- $\alpha$ -ionone, and a woody, cedarwood-type odour with a threshold of 20–40 ppb for its enantiomer. These olfactory differ-

Table 7. Odour descriptions of irone samples according to Ref. 103

Compound	Odour description	Odour threshold
(+)-104a	Violet like, with woody, methylionone undertones	100 ppm <sup>a</sup>
(-)-104a	Slightly stronger with a distinct 'orris-butter' character	10 ppm <sup>a</sup>
(+)-104b	It was described as the weakest of the $\alpha$ -isomers	
(-)-104b	It shows a weak violet/wood/red berry character. Neither (+)- nor (-)- <i>trans</i> - $\alpha$ -irone possesses the characteristic 'orris' odour	
(+)-106a	It shows a floral, fatty, sweet, and woody odour character, an ionone-type odour with slightly sweet aspects	> 100 ng/l <sup>b</sup>
(-)-106a	It shows a $\beta$ -ionone-type odour of warm floral-woody tonality. Green aspects are present, too. It shows some fruity nuances, reminiscent of pineapples. The odour is linear, and it can be considered a dry-down note	0.75 ng/l <sup>b</sup>
(+)-106b	It is very weak, of a woody odour tonality	113.5 ng/l <sup>b</sup>
(-)-106b	It is not very powerful, but it possesses a soft 'orris-butter'-type of odour	26.35 ng/l <sup>b</sup>
(+)-105	It possesses a $\beta$ -ionone-type odour of warm floral-woody tonality with green and anisic aspects. The odour is linear, and the tenacity of the note is good. It can be considered a dry-down note	
(-)-105	It has a woody odour with a distinct honey note, that is quite sweet. Besides, it shows floral ionone-type facets, and a fruity tonality, but also an unpleasant smoky character. It belongs to the $\beta$ -ionone-type family, without being very close to $\beta$ -ionone	

<sup>a</sup> Odour threshold by triangular test.<sup>b</sup> Odour threshold by GC olfactometry.

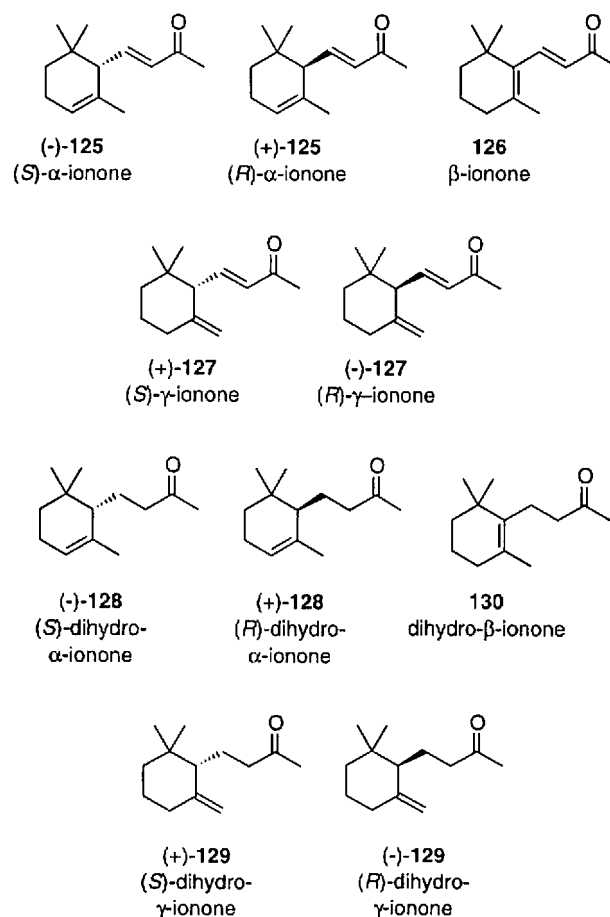
ences were confirmed by perfumers of Firmenich in 1992.<sup>110</sup> Perfumers of Givaudan<sup>104</sup> found the odour characteristics of the racemate and both enantiomers quite close, and they determined slightly different odour threshold by GC/olfactometry. The data were confirmed using chiral phases: (*S*)-(-)- $\alpha$ -ionone odour threshold=2.7 ng/l of air, (*R*)-(+)- $\alpha$ -ionone odour threshold=3.2 ng/l of air, ( $\pm$ )- $\alpha$ -ionone odour threshold=3.0 ng/l of air.

$\alpha$ -Ionone samples often contain traces of  $\beta$ -ionone, which is characterised by a high rate of anosmia: 34% of European people cannot smell it. This can partly justify the differences in the odour quality of  $\alpha$ -ionone enantiomers reported in the literature. The purity of the samples is then a great source of error. For this reason, odour thresholds are better measured by GC/olfactometry using chiral phases.

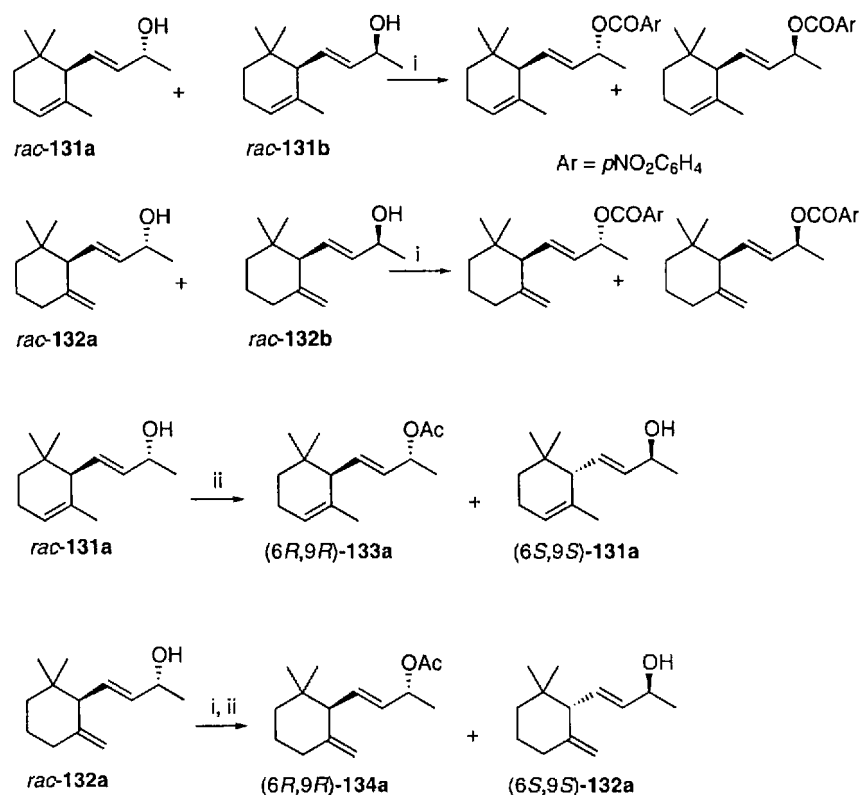
Our research in the field of ionones allowed us to have in hand both enantiomers of  $\alpha$ -ionone **125**,  $\gamma$ -ionone **127**, dihydro- $\alpha$ -ionone **128**, and dihydro- $\gamma$ -ionone **129** with high enantiomeric excess and chemical purity, prepared by enzymic procedures.<sup>104,111</sup>

Dihydro- $\beta$ -ionone **130** was included in the study for the sake of completeness. The same strategy was employed for  $\alpha$  and  $\gamma$ -ionones (Scheme 33).<sup>111a,c</sup> The two mixtures of diastereoisomeric  $\alpha$ -ionols **131a,b** and  $\gamma$ -ionols **132a,b** were separated by fractional crystallisation of the corresponding *p*-nitrobenzoate esters. Ionols **131a** and **132a** were recovered as pure diastereoisomers and submitted to lipase acetylation. Enantiopure acetates (6*R*,9*R*)-**133a** and (6*R*,9*R*)-**134a**, and alcohols (6*S*,9*S*)-**131a** and (6*S*,9*S*)-**132a** were then converted into the corresponding enantiopure ionones. Enantiopure dihydroionones **128** and **129** were obtained by catalytic reduction of the corresponding ionone isomers. Olfactory evaluation of all these derivatives was performed

by an expert perfumer (Givaudan) on blotter over a period of 24 h, and detection odour thresholds were measured by GC/olfactometry. The results are collected in Table 8. Except for  $\alpha$ -ionone, there is at least a difference of one order of magnitude between the







**Scheme 33.** Reagents and conditions: (i) *p*-nitrobenzoyl chloride, pyridine; crystallisation from hexane; (ii) lipase PS, *t*-butyl methyl ether, vinyl acetate.

threshold values of the enantiomeric pairs, and even three orders of magnitude in the case of  $\gamma$ -ionone. (*S*)-(+)- $\gamma$ -Ionone is the most powerful and most pleasant odorant of the investigated ionones.

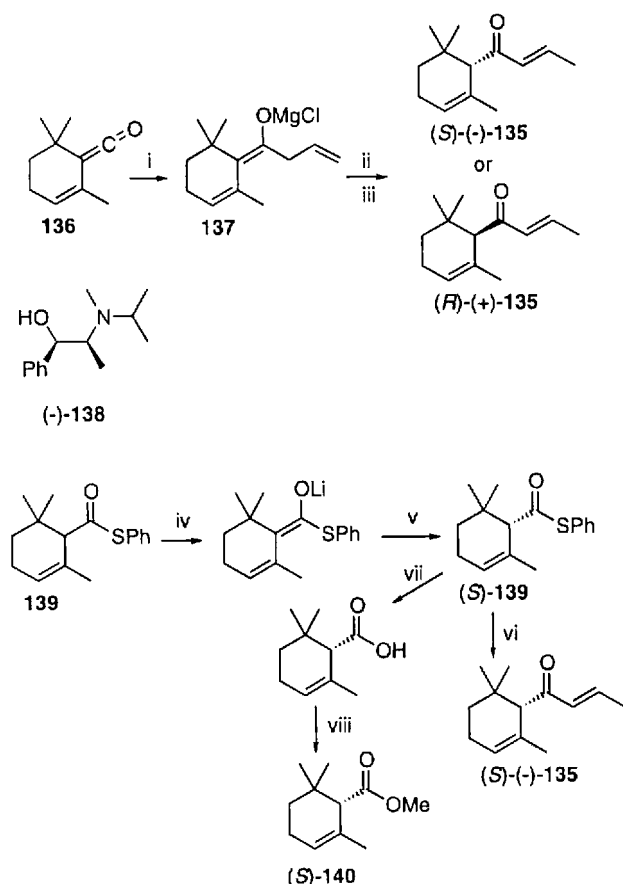
#### 4.4. Damascones

**$\alpha$ -Damascone.**  $\alpha$ -Damascone **135** belongs to the class of the so-called 'rose ketones'. It was first synthesised in 1970,<sup>112</sup> and then found in black tea.<sup>113</sup> It is an impor-

tant perfume constituent, being characterised by a *powerful fresh-fruity note with a rose-like character*. Fehr and Galindo reported<sup>114</sup> on the synthesis of both enantiomers of  $\alpha$ -damascone. Reaction of ketene **136** with allylmagnesium chloride gave enolate **137** which was treated with (–)-**138**-Li and protonated with (–)-**138**-H, to afford (*S*)-**135** with ee = 84% (ee = 95% after crystallisation) (Scheme 34). The use of (+)-**138**-Li and of (+)-**138**-H allowed the synthesis of (*R*)-**135** with ee = 84% (ee = 98% after crystallisation). A few years later the procedure of enantioselective protonation was

**Table 8.** Odour descriptions of ionone samples according to Ref. 104

Compound	Olfactory description	Odour threshold (ng/l of air)
(+)- <b>125</b>	Floral-woody note, with an additional honey aspect. Slightly weaker than the (–)-isomer	3.2
(–)- <b>125</b>	Floral-woody note, with an additional honey aspect. Slightly more powerful than the ( <i>R</i> )-(+)-isomer	2.7
(±)- <b>125</b>	Floral-woody note, with an additional honey aspect	3.0
<b>126</b>	Typical floral-woody note	0.12
(–)- <b>127</b>	Weak green, fruity, pineapple-like odour with metallic aspects, quite different from the typical ionone odour; however, also slightly woody, ionone-type nuances are present	11
(+)- <b>127</b>	Linear, very pleasant, floral, green, woody odour with a very natural violet tonality; the most powerful and pleasant isomer	0.07
(+)- <b>128</b>	Floral, violet-type odour with slightly fruity aspects. It possesses also a woody side, but less pronounced than in dihydro- $\beta$ -ionone	31
(–)- <b>128</b>	Exhibits a floral orris-type odour, with woody aspects and a distinct honey note	100
(–)- <b>129</b>	Emanates a fatty, earthy odour with floral, orris-type nuances	6.2
(+)- <b>129</b>	Fatty-floral odour, less orris-type than the other compounds of the dihydro series. An animalic undertone is also present	39
<b>130</b>	It possesses a $\beta$ -ionone-type odour of floral-woody, orris-type tonality, with green, earthy undertones	1.7



**Scheme 34.** Reagents and conditions: (i)  $\text{CH}_2=\text{CHCH}_2\text{MgCl}$ ; (ii) chiral proton source; (iii)  $\text{Al}_2\text{O}_3$ ,  $\text{Et}_2\text{O}$ ; (iv)  $\text{BuLi}$ ; (v)  $(-)-138$ ; (vi)  $\text{CH}_2=\text{CHCH}_2\text{Cl}$ ,  $\text{LDA}$ ,  $\text{THF}$ ;  $p$ - $\text{TosOH}$ , toluene; (vii)  $\text{H}_2\text{O}_2$ ,  $\text{LiOH}$ , aq.  $\text{EtOH}$ ; (viii)  $\text{K}_2\text{CO}_3$ ,  $\text{MeI}$ , acetone.

improved<sup>115</sup> by using ester enolates as intermediates. Treatment of phenyl thiol ester **139** with  $\text{BuLi}$ , followed by protonation with  $(-)/(+)-138$  afforded  $(S)/(R)-139$

with  $\text{ee}=99\%$ . These enantiomers were employed to prepare enantiopure  $\alpha$ -damascones and enantiopure  $\alpha$ -cyclogeranic acid methyl esters **140**.<sup>116</sup>

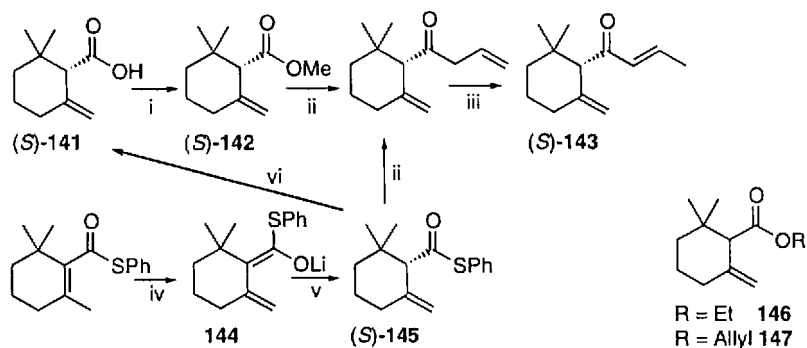
The organoleptic properties of the two enantiomers of  $\alpha$ -damascone were found to be quite different, especially for the values of the odour thresholds. The  $(S)-(-)-135$  (odour threshold = 1.5 ppb) was described as *more floral, reminiscent of rose petals, also having a winy character, without the corn and green apple note found in the  $(R)$ -enantiomer* (odour threshold = 100 ppb).<sup>31c</sup>

$(R)-140$  was described by Fehr et al. to show a *precious flowery, fruity, damascone-like fragrance*, whereas  $(S)-140$  was found to be characterised by a *green, metallic, minty, camphoraceous note*.<sup>115</sup>

In a further development of this work on damascones,  $(R)$ - and  $(S)-141$  were obtained by fractional crystallisation of the corresponding diastereoisomeric phenylethylamine salts, and then converted into the enantiomers of methyl  $\gamma$ -cyclogeranic **142** and of  $\gamma$ -damascone **143** (Scheme 35).  $(+)-$  and  $(-)-142$  and  $(+)-$  and  $(-)-143$  were also prepared according to the usual procedure of enantioselective protonation of enolates (Scheme 35).<sup>117</sup> Protonation of thiol ester enolate **144** with  $(-)$ - or  $(+)-N$ -isopropylephedrine **138** and subsequent hydrolysis of the  $(R)$ - and  $(S)-S$ -phenyl- $\gamma$ -thiogercanate **145**, afforded  $(R)$ - and  $(S)-141$ . Treatment of the enantiomers of **145** with allylmagnesium chloride, followed by isomerisation of the terminal double bond, yielded  $(R)$ - and  $(S)-143$ . The organoleptic evaluations of enantiopure samples of  $(R)$ - and  $(S)-141$ , and  $(R)$ - and  $(S)-142$ , and of other esters of  $\gamma$ -cyclogeranic acid **146** and **147** (Table 9) revealed that the  $(S)$ -series possessed excellent fruity-floral, aromatic odour qualities, whereas the  $(R)$ -series showed a more common profile containing undesired notes.

#### 4.5. Rose oxide and Doremox®

The two diastereoisomeric rose oxides  $(2S,4R)\text{-cis-148a}$  and  $(2R,4R)\text{-trans-148b}$  were discovered in rose oil<sup>118</sup>

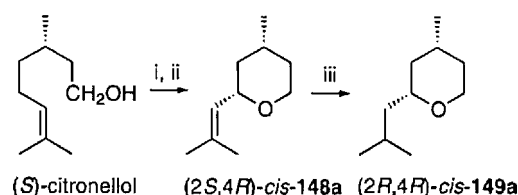


**Scheme 35.** Reagents and conditions: (i)  $\text{MeI}$ , acetone,  $\text{K}_2\text{CO}_3$ ; (ii) allyl magnesium chloride,  $\text{LDA}$ ,  $\text{THF}$ ; (iii)  $\text{Al}_2\text{O}_3$ ,  $\text{Et}_2\text{O}$ ; (iv)  $\text{LDA}$ ,  $\text{THF}$ ,  $-78^\circ\text{C}$ ; (v)  $(+)-138$ ; (vi)  $\text{H}_2\text{O}_2$ ,  $\text{LiOH}$ , aq.  $\text{EtOH}$ .

Table 9. Odour properties of damascones and derivatives

Compound	Odour description
(S)-142	Aromatic, damascone-like, thujone, fruity
(R)-142	More common than (S)-142, camphoraceous, corky, cellar
(S)-146	Aromatic, fruity, damascone-like
(R)-146	Less fruity, aromatic, rosemary, less powerful than (S)-146
(S)-147	Green, floral, blackcurrant, aromatic, fruity, pleasant
(R)-147	More green, less blackcurrant, less floral, weaker than (S)-147
(S)-143	Nice damascone character, camphoraceous
(R)-143	Liquorice, damascone-like, camphoraceous, inferior to (S)-143

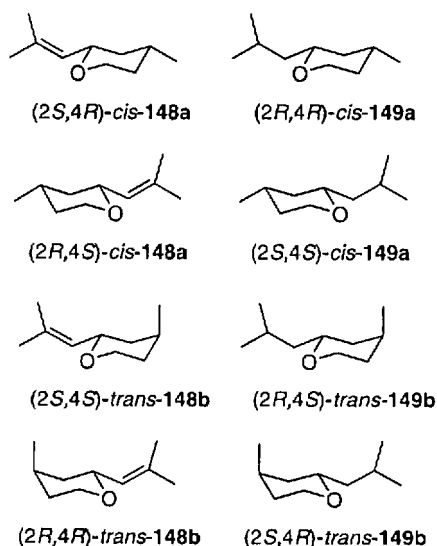
and geranium oil<sup>119</sup>, and, after the optimisation of an efficient synthetic procedure<sup>120</sup> starting from (–)-citronellol, found great applications in the field of perfumery. In general, rose oxide has a *refreshing, floral, green note*. However, the fragrance delicately varies from isomer to isomer. That is to say, *cis*-rose oxide has a *green note just like geranium and peppermint*, while *trans*-rose oxide has a *somewhat intense fragrance compared with the cis-isomer*. In 1972 Ohloff<sup>121</sup> synthesised and evaluated the enantiomers of *cis*-rose oxide. (2*S*,4*R*)-148a was found to have a *sweet and floral fragrance with an intense green note*. (2*R*,4*S*)-148a had a *somewhat spicy note*. Only recently, Matsuda et al. found that (2*S*,4*R*)-148a had a threshold of 0.5 ppb, 100 times lower than that of the enantiomer (2*R*,4*S*)-148a.<sup>122</sup> In the same work dihydro derivatives 149a and 149b were prepared. These derivatives had been described to have a fragrance similar to that of rose oxide, but to be much more stable to heat, acids and light than rose oxide itself. The enantiomers of 148a,b and 149a,b were prepared according to Scheme 36, starting from (S)- and (R)-citronellol. The complete sensory properties are reported in Table 10. A study of



Scheme 36. Reagents and conditions: (i) Na<sub>2</sub>CO<sub>3</sub>, Br<sub>2</sub>, acetonitrile, Aliquat, KOH; (ii) 30% H<sub>2</sub>SO<sub>4</sub>; fine distillation; (iii) Ni-Raney, ethanol.

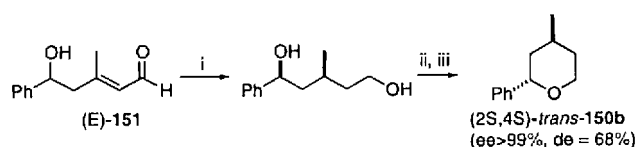
Table 10. Odour properties of rose oxide and dihydrorose oxide stereoisomers

Compound	Odour description	Odour threshold (ppb)
(2 <i>S</i> ,4 <i>R</i> )-148a	Floral, green, clean, sharp, light, rose green, diffusible, strong	0.5
(2 <i>R</i> ,4 <i>R</i> )-148b	Floral green, green herbal, minty, fruity	160
(2 <i>R</i> ,4 <i>S</i> )-148a	Herbal, green, floral, hay green, earthy, heavy	50
(2 <i>S</i> ,4 <i>S</i> )-148b	Herbal, green, floral, fruity, herbal, rose, citrus (bitter peel)	80
(2 <i>R</i> ,4 <i>R</i> )-149a	Floral, green, clean, fruit, herbal, rose, green, leafy	17
(2 <i>S</i> ,4 <i>R</i> )-149b	Herbal, floral, fruity, minty, dusty, floral, green	150
(2 <i>S</i> ,4 <i>S</i> )-149a	Herbal, green, leafy, heavy	450
(2 <i>R</i> ,4 <i>S</i> )-149b	Herbal, green citrus, fruity, herbal fresh, citrus, grapefruit	160

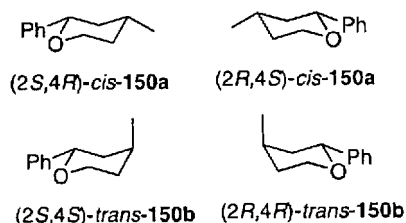


biodegradability of rose oxide was also performed. (2*S*,4*R*)-148a and (2*R*,4*R*)-148b exclusively show biodegradability, while the (4*S*)-enantiomers were hardly degradable. Between the (4*R*)-isomers, (2*S*,4*R*)-148a degraded at a rate several times higher than that of the (2*R*,4*R*)-*trans* isomer.

An evolution in the structure–activity study of the olfactory properties of rose oxide was represented by the preparation of 4-methyl-2-phenyltetrahydro-2*H*-pyran Doremox<sup>®</sup>, 150 by Firmenich.<sup>123</sup> The compound was obtained as a mixture of the two racemic *cis*-150a and *trans*-150b diastereoisomers, by hydrogenation of 5,6-dihydro-4-methyl-2-phenyl-2*H*-pyran in the presence of Pd on charcoal. The isobutenyl fragment of 148 was substituted with a phenyl group, in order to increase the substantivity of rose scent, i.e. the persistence of the perfume material on blotters, skin, or in the various applications.<sup>32b</sup> The phenyl group increases the mass, and thus the vapour pressure, without a substantial change of the shape of the molecule, which would otherwise affect the main odour characteristics.



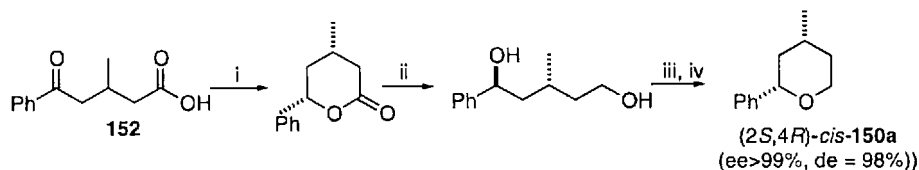
**Scheme 37.** Reagents and conditions: (i) Baker's yeast; (ii)  $\text{CHCl}_3$ ,  $p$ -TosCl, pyridine; (iii) MeONa, MeOH.



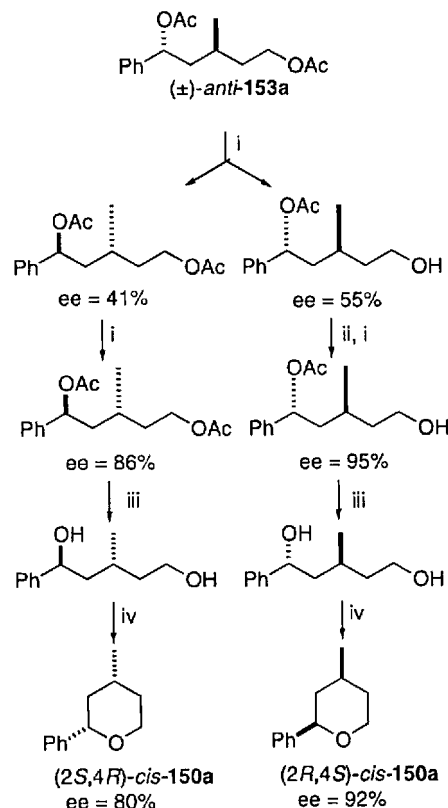
The two isomers **150a** and **150b** were separated by preparative gas chromatography, and their odour properties were described.<sup>123</sup> The racemic *cis* diastereoisomer was found to be very powerful and to have a green, rose-oxide-diphenyl oxide type note. The racemic *trans* isomer had a much weaker odour, with a green, vegetable, slightly dirty and minty character and a floral undertone.

We accomplished the preparation of all the four enantiomerically enriched isomers of Doremox® by biocatalysed routes.<sup>124</sup> Baker's yeast reduction of suitable precursors, unsaturated aldehyde **151** and keto acid **152** was enantiospecific and highly diastereoselective (Schemes 37 and 38). Diol precursors of (2S,4S)-(+)-**150b** (ee >99%, de = 68%) (Scheme 37), and of (2S,4R)-(-)-**150a** (ee >99%, de = 98%) (Scheme 38) could be obtained when a carbon-carbon double bond or a carbonyl was reduced by yeast, under the influence of a pre-existing stereocentre in position  $\beta$ . A second approach was based on lipase-mediated hydrolysis of diacetates **153a** and **153b**, according to Schemes 39 and 40. Olfactory evaluation of Doremox® samples gave the following results:

(2R,4S)-cis-**150a**, ee = 92%, de >99%: rose oxide, diphenyl oxide, metallic, slightly plastic.  
(2S,4R)-cis-**150a**, ee = 80%, de >99%: rose oxide, powerful, nice.



**Scheme 38.** Reagents and conditions: (i) Baker's yeast; (ii)  $\text{LiAlH}_4$ , THF; (iii)  $\text{CHCl}_3$ ,  $p$ -TsCl, pyridine; (iv) MeONa, MeOH.



**Scheme 39.** Reagents and conditions: (i) Lipase PS, THF-water, pH 7.8, NaOH 0.025 M; column chromatography; (ii) acetic anhydride, pyridine; (iii) KOH, MeOH; (iv)  $p$ -TsCl, pyridine, then MeONa in methanol.

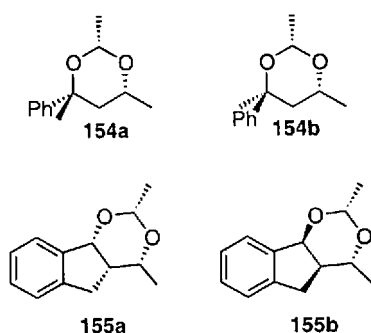
(2S,4S)-trans-**150b**, ee = 72%, de = 70%: weak, rosy, plastic, citronellol, a rose oxide note is also present.  
(2R,4R)-trans-**150b**, ee = 50%, de = 77%: rosy, rose oxide, metallic, off note.

(2S,4R)-cis-**150a** is, thus, the nicest and the most powerful isomer of the series. This stereoisomer, incidentally, has the same absolute configuration of the most appreciated of rose oxide isomers, i.e. (2S,4R)-cis-**148a**.

#### 4.6. Magnolan® and Floropal®

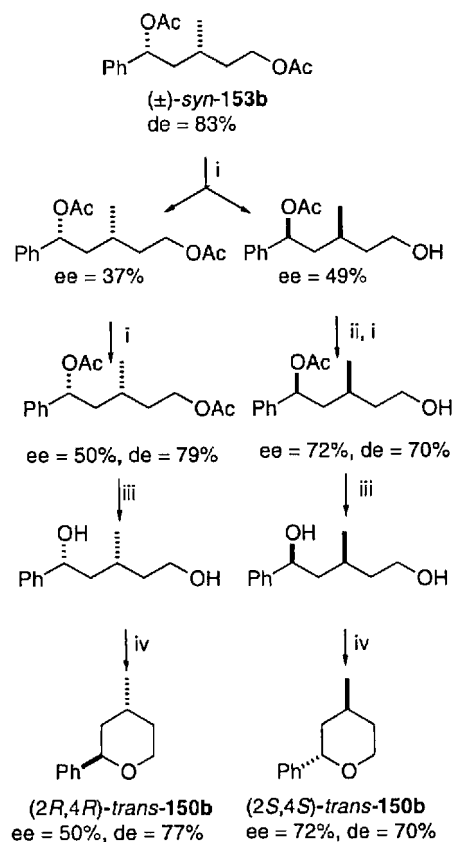
Floropal® or Vertacetal®, **154**, and Magnolan® **155** are two 1,3-dioxane odorants. Floropal is a grapefruit fragrance with fruity rhubarb undertones;<sup>32b</sup> Magnolan is a

substantive floral, rosy odorant which is employed to convey the freshness of rose flower dew in perfume compositions.<sup>32b</sup> They are both prepared for commercial purpose as mixtures of two racemic diastereoisomers by Prins reaction of  $\alpha$ -methyl styrene and indene, respectively, with acetaldehyde.<sup>125,126</sup> The mixture of **154a** and **154b** has been employed for more than 20 years as a fragrance and sold under the names Vertacetal® (Dragoco Gerberding & Co. AG, Holzminden) and Floropal/Corps 717 (Haarmann & Reimer GmbH, Holzminden). The odour of Vertacetal® is described as 'fresh-herbal, typically the impression of grapefruit', and the aroma of Floropal/Corps 717 is said to be 'herbal-fresh, floral-green, similar to chrysanthemum, cyprus, and grapefruit'. In 2000 Pickenhagen et al.<sup>127</sup> reported the sensory properties of the two racemic diastereoisomers **154a** and **154b**.



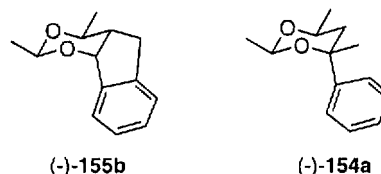
**154a** was described as strong, herbal-fresh, green, and typical grapefruit; **154b** was found to be very weak, chemical solvent-like, and to have a detracting influence upon the odour properties of the mixture. GC analysis highlighted that the two commercial products were different with respect to the amount of the two diastereoisomers:<sup>127</sup> Vertacetal contained 54.38% of **154a** and 44.33% of **154b**, while Floropal contained 63.71% of **153a** and 34.52% of **154b**. The mixture was enriched into the more valuable derivative **154a**, either by fractional distillation or by reaction with  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ . On the basis of this interesting stereoselectivity in the odour perception of dioxane odorants, we undertook the enzyme-mediated synthesis of the enantiomers of the Magnolan and Floropal diastereoisomers, in order to investigate the olfactory response of each single isomer. Key steps were the lipase-catalysed irreversible transesterifications of alcohol **156** and of diols **157a**, and **157b**.<sup>128</sup>

Treatment of racemic alcohol **156** with Lipase PS gave enantiopure acetate (*R*)-**158** and alcohol (*S*)-**156**, which were converted, separately, into mixtures of enantiomerically enriched diastereoisomeric diols **159a** and **159b** (Scheme 41). These latter diols were submitted to ketalisation, in order to afford the corresponding Floropal isomers. (*S*)-**156** was also obtained by Baker's yeast reduction of diketone **160**. Lipase PS-mediated acetylation of the mixture of diols (2*R*,4*R*)-**159b** and (2*S*,4*R*)-**159a** was diastereoselective and gave access to the single Floropal isomer (2*R*,4*R*,6*R*)-**154b**.

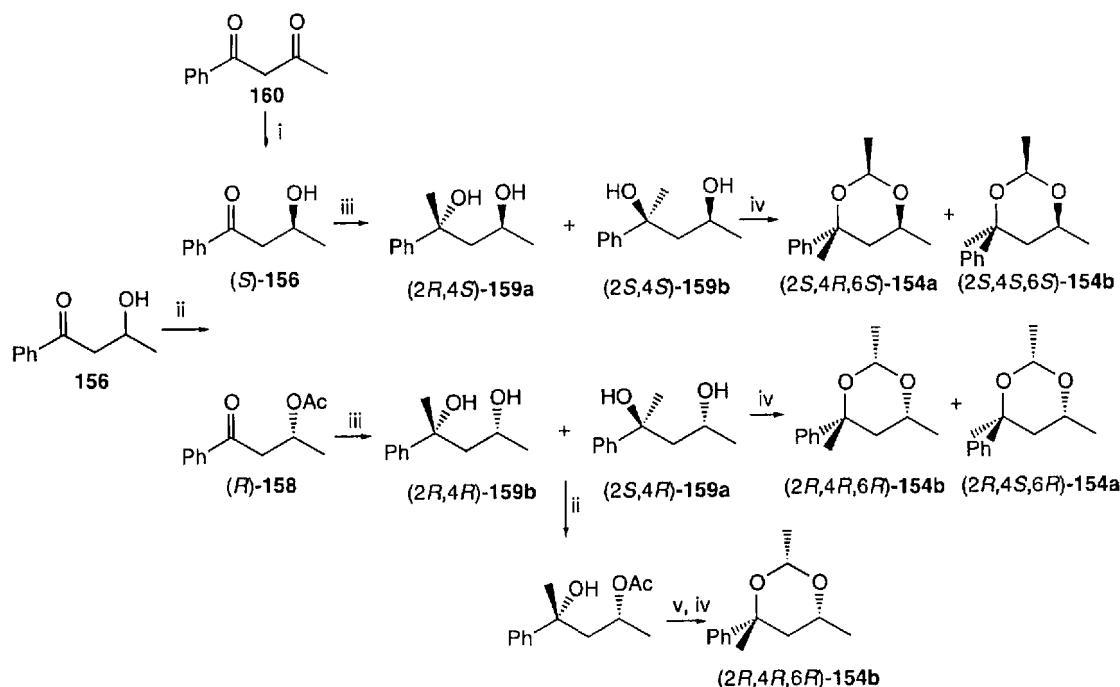


**Scheme 40.** Reagents and conditions: (i) Lipase PS, THF-water, pH 7.8, NaOH 0.025 M; column chromatography; (ii) acetic anhydride, pyridine; (iii) KOH, MeOH; (iv) *p*-TsCl, pyridine, then MeONa in methanol.

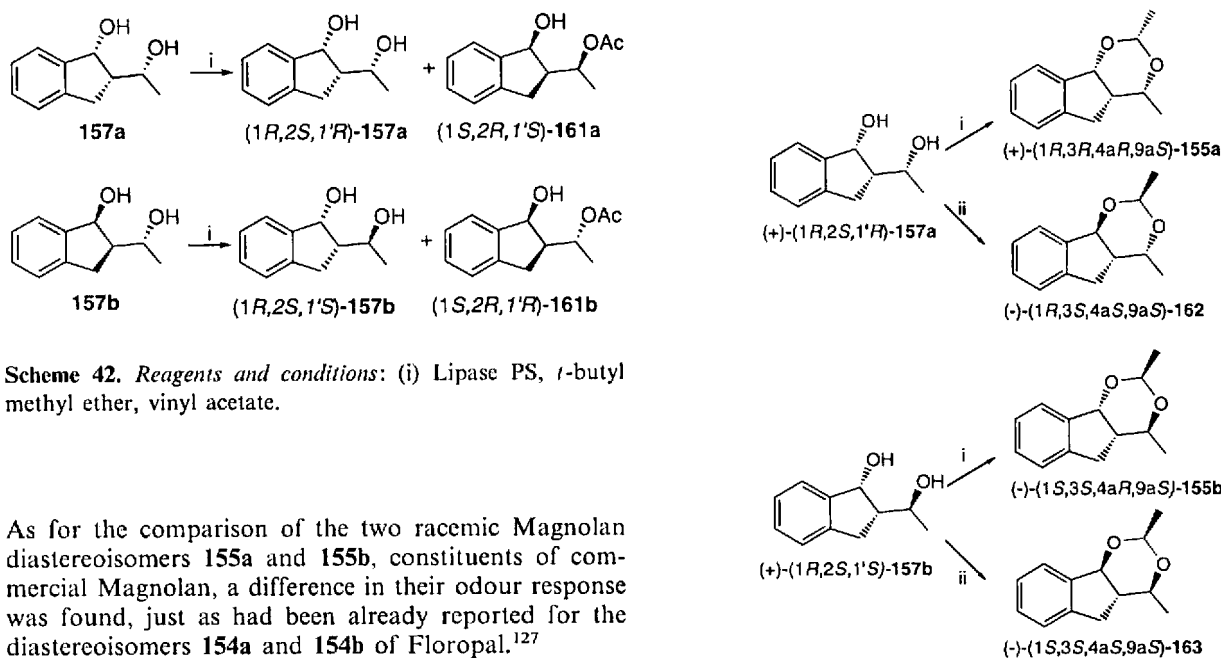
Kinetic resolution of diols **157a** and **157b** gave alcohols (1*R*,2*S*,1'*R*)-**157a** and (1*R*,2*S*,1'*S*)-**157b**, and monoacetates (1*S*,2*R*,1'*S*)-**161a** and (1*S*,2*R*,1'*R*)-**161b** (Scheme 42). The four enantiomerically enriched diols **157a** and **157b** were converted into Magnolan stereoisomers, by reaction with acetaldehyde in the presence of pyridinium *p*-toluenesulphonate in  $\text{CH}_2\text{Cl}_2$  (Scheme 43). When *p*-toluenesulphonic acid was employed, ketalisation afforded the enantiomers of the 'new' Magnolan diastereoisomers **162** and **163**, by inversion of the configuration at the benzylic carbon atom.



The following sensory data were collected. As for Floropal samples, (2*S*,4*R*,6*S*)-(-)-**154a** was found to be the most interesting of the enantiomers of the most appreciated diastereoisomer **154a**: it was described as typically Vertacetal, with a characteristic rhubarb note. Its presence confers to the mixture (2*S*,4*R*,6*S*)-**154a**/(2*S*,4*S*,6*S*)-**154b** (1:2) a nice character, in spite of the fact that the major component is (2*S*,4*S*,6*S*)-**154b**.



**Scheme 41.** Reagents and conditions: (i) Baker's yeast; (ii) Lipase PS, *t*-butylmethylether, vinyl acetate; (iii)  $\text{CH}_3\text{MgI}$ ,  $\text{Et}_2\text{O}$ ; (iv)  $\text{CH}_3\text{CHO}$ ,  $\text{CH}_2\text{Cl}_2$ , *p*-TsOH; (v)  $\text{KOH}$ ,  $\text{MeOH}$ .



**Scheme 42.** Reagents and conditions: (i) Lipase PS, *t*-butyl methyl ether, vinyl acetate.

As for the comparison of the two racemic Magnolan diastereoisomers **155a** and **155b**, constituents of commercial Magnolan, a difference in their odour response was found, just as had been already reported for the diastereoisomers **154a** and **154b** of Floropal.<sup>127</sup>

(±)-**155a** was found richer than commercial Magnolan, less plastic and more floral.

(±)-**155b** was described to be more powerful, much fresher than (±)-**155a**, and with an additional pleasant marine tonality, also more substantive on blotter than (±)-**155a**. As for the two enantiomers of **155b**, (+)-**155b** was described as weak, acidic, floral, rosy, sweet, warm, whereas (–)-**155b** was highly appreciated and found rosy, floral (geranium, magnolia), citronellyl acetate,

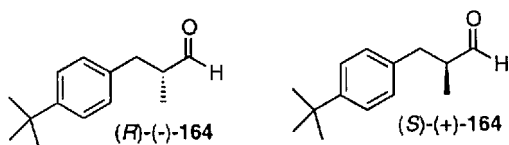
**Scheme 43.** Reagents and conditions: (i)  $\text{CH}_3\text{CHO}$ ,  $\text{CH}_2\text{Cl}_2$ , pyridium *p*-toluenesulphonate; (ii)  $\text{CH}_3\text{CHO}$ ,  $\text{CH}_2\text{Cl}_2$ , *p*-TsOH.

citric-fruity, with a slight green nuance. (–)-**155b** is the most interesting enantiomer of diastereoisomer **155b**. The relative configuration is the same observed in (–)-**154a**, the most appreciated of **154a** enantiomers. (+)-

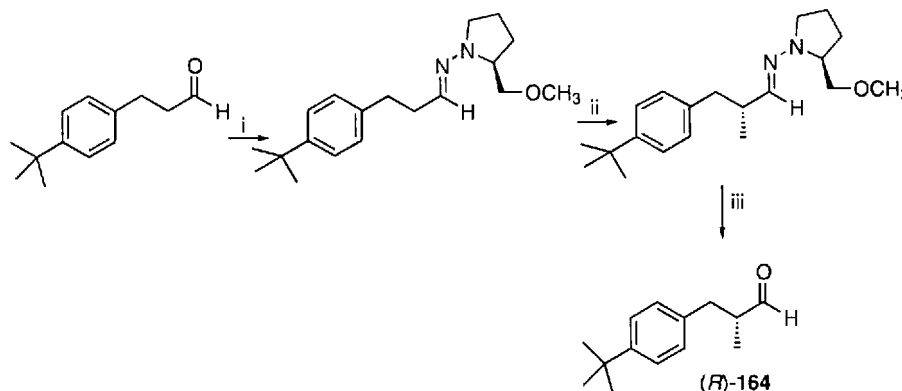
and (–)-**162**, and (+)- and (–)-**163** did not show any value as fragrant substances.

#### 4.7. Lilial® and Florhydral®

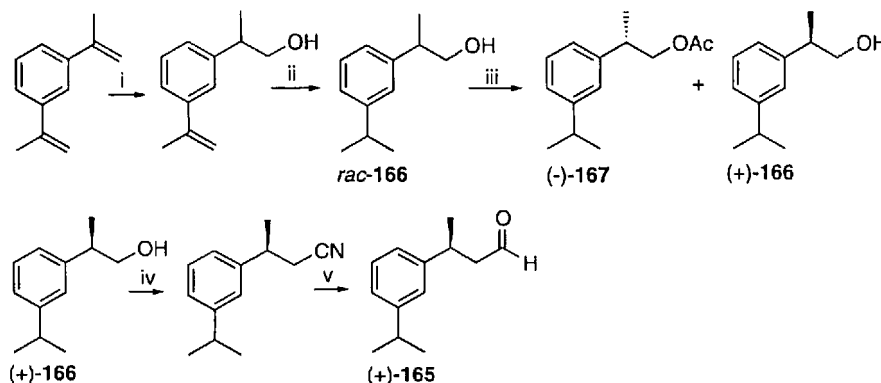
Lilial® **164** is one of the most widely employed muguet-type odorant. It shows a *very powerful, fresh, floral note, reminiscent of lily of the valley, lindlenblossom, and cyclamen*.<sup>32a</sup> The two enantiomers of lilial were prepared by Enders and Dyker,<sup>129</sup> making use of the SAMP/RAMP hydrazone procedure (Scheme 44), and submitted to olfactory evaluation. (*R*)-(–)-lilial (ee = 95%) was described as *stronger and more aggressive than the racemate, top scent a little more watery*. (*S*)-(+)-Lilial (ee = 93%) was found a *little softer and less expressive than the racemate*. Thus (–)-**164** was described as the most intense, but both enantiomers smelled of lily of the valley.



3-(3-Isopropylphenyl)butanal **165**, commercialised by Givaudan with the trade name of Florhydral®, was introduced into perfumery as a 'super lilial', because it is much stronger than lilial.<sup>62</sup> However, its smell is *not only lilial and lily of the valley in nature, but it has also some interesting ozonic aspects. It is powerful and diffusive, and it can be used to give long lasting fresh, and green top notes, and to convey a marine and ozonic touch to perfume compositions*. We optimised a biocatalysed synthesis of the enantiomers of **165**, based on the lipase-mediated kinetic resolution of a suitable alcohol intermediate **166** (Scheme 45).<sup>130</sup> Acetate (–)-**167** and alcohol (+)-**166** were thus recovered, and converted into (–)- and (+)-**165**. The two enantiopure samples of (+)-**165** and (–)-**165** were submitted to skilled perfumers (Givaudan) for the olfactory evaluation and the following descriptions were obtained. (+)-**165** (ee > 99%) was found to be *floral, watery, green, yet with acidic touch, even in the dry down note*. In comparison with racemic **165**, this enantiomer is *more green, a bit less watery, and more powerful* (odour threshold = 0.035 ng/l air). Enantiomer (–)-**165** (ee > 99%) has a *typical Florhydral smell, floral, fresh, green, muguet-like, but more marine, and more plastic* (odour threshold = 0.88 ng/l air). As in the

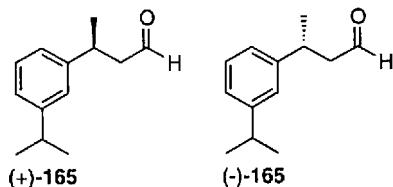


Scheme 44. Reagents and conditions: (i) (*S*)-1-amino-2-(methoxymethyl)pyrrolidine; (ii) LDA; Et<sub>2</sub>O; (CH<sub>3</sub>)<sub>2</sub>SO<sub>4</sub>; (iii) excess CH<sub>3</sub>I; HCl 4N, *n*-pentane.



Scheme 45. Reagents and conditions: (i) BH<sub>3</sub>(CH<sub>3</sub>)<sub>2</sub>S, THF; then NaOH–H<sub>2</sub>O<sub>2</sub>; (ii) H<sub>2</sub>, Pd/C; (iii) PPL, *t*-butylmethyl ether, vinyl acetate; column chromatography; (iv) TosCl, pyridine; then NaCN in DMSO; (v) diisobutylaluminium hydride in THF.

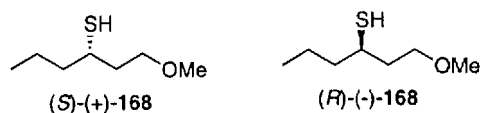
case of linal, a more notable difference was found in the odour strength of the two enantiomers, rather than in their odour quality. The intensity difference of florhydral samples was quite remarkable, being the perception threshold of (–)-165 25 times higher than that of the (+)-isomer.



### 5. Sulphur odorants

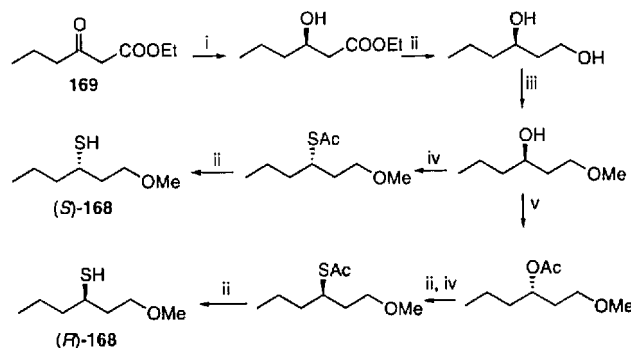
*“And, most dear actors, eat no onions nor garlic,  
for we are to utter sweet breath”*  
(W. Shakespeare, A Midsummer Night’s Dream, Act IV, Scene II)

1-Methoxyhexane-3-thiol **168** was identified as the component responsible of the peculiar odour signal elicited by flowering clary-sage plants (*Salvia sclarea* L.), and was described as *both intriguing and repulsive, somewhat reminiscent of human axillary perspiration*.<sup>131</sup> The enantioselective synthesis of the two enantiomers of **168** was accomplished by a strategy (Scheme 46) involving the Baker’s yeast reduction of keto ester **169**, and the procedure of Küntzel and Frater<sup>132</sup> for the introduction of the sulphur functionality. (S)-**168** was found to have *strong connotations of burnt sulphur and alliaceous notes, and evoked associations with human axillary perspiration*. (R)-**168** was perceived as *sulphury, herbaceous, and onion-like, and definitely lacked the unique clary-sage signal*. (S)-**168** showed a detection threshold of  $0.04 \cdot 10^{-3}$  ng/l air, which is one of the lowest value ever recorded, and is 25 times lower than that of (R)-**168** ( $1.09 \cdot 10^{-3}$  ng/l air). The (S)/(R) ratio in natural **168** is 6:4.



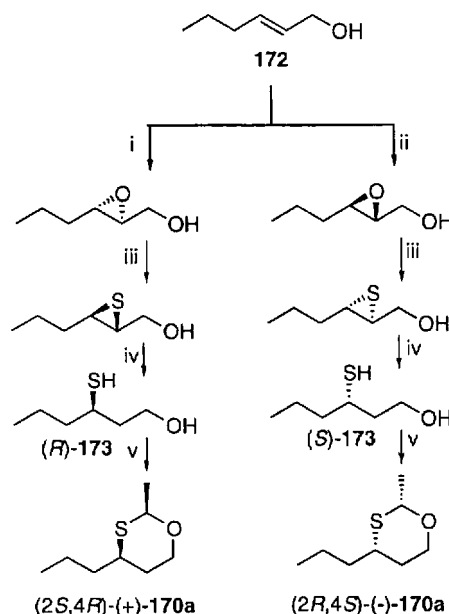
1-Methoxyhexane-3-thiol **168** belongs to a class of strong odorants showing the *O*- and *S*-functionalities in 1,3 position. Other interesting molecules of the same class are 2-methyl-4-propyl-1,3-oxathiane **170**, and 3-mercapto-2-methylpentanol **171**.

2-Methyl-4-propyl-1,3-oxathiane **170** was isolated as a 10:1 mixture of *cis/trans* isomers from the juice of the yellow passionfruit (*Passiflora edulis* f. *flavicarpa*) by Winter et al.<sup>133</sup> Pickenhagen et al.<sup>134</sup> reported on the enantioselective synthesis of (+)- and (–)-*cis*-**170a**, based on the Sharpless epoxidation of (*E*)-2-hexen-1-ol **172**, using diethyl (+)- and (–)-tartrate, respectively



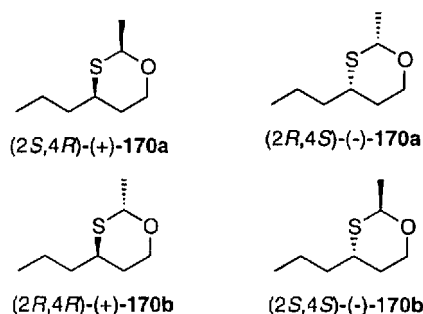
**Scheme 46.** Reagents and conditions: (i) Baker’s yeast; (ii)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ ; (iii)  $\text{KH}$ ,  $\text{MeI}$ ,  $\text{THF}$ ; (iv)  $\text{Ph}_3\text{P}$ , diisopropyl azodicarboxylate,  $\text{AcSH}$ ,  $\text{THF}$ ; (v)  $\text{Ph}_3\text{P}$ , diisopropyl azodicarboxylate,  $\text{AcOH}$ ,  $\text{THF}$ .

(Scheme 47). (+)- and (–)-*cis*-**170a** were described as powerful odorants, with threshold values in water of 2 and 4 ppb, respectively. The odour of (2*S*,4*R*)-(+)-**170a** on a smelling strip was found to be *typical sulphurous, with a rubbery onion note, and a fruitiness reminiscent of grapefruit peel, mango and passionfruit*. (2*R*,4*S*)-(–)-**170a** was found *weaker, without the pronounced sulphur character of the enantiomer, but characterised by a fresh note with more iris character*. In water solution at 0.1 ppm concentration, (2*S*,4*R*)-(+)-**170a** possessed the *typical sulphur notes of tropical fruits*, whereas (2*R*,4*S*)-(–)-**170a** was *slightly camphoraceous, more woody, and not very typical of tropical fruits*.



**Scheme 47.** Reagents and conditions: (i) (+)-diethyl tartrate,  $\text{Ti}(\text{OCHMe}_2)_4$ ,  $(\text{CH}_3)_3\text{COOH}$ ; (ii) (–)-diethyl tartrate,  $\text{Ti}(\text{OCHMe}_2)_4$ ,  $(\text{CH}_3)_3\text{COOH}$ ; (iii)  $\text{NH}_2\text{CSNH}_2$ ; (iv)  $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ ; (v)  $\text{CH}_3\text{CHO}$ ,  $\text{H}_3\text{O}^+$ .





Mosandl prepared<sup>135</sup> all the four stereoisomers of 1,3-oxathianes **170a,b** in enantiopure form, and described<sup>136</sup> their sensory characteristics. A key step of the synthetic procedure was the resolution of derivative **173**: the primary alcoholic function of **173** was protected and the 3-mercapto group esterified with chiral acyl chlorides (e.g. (–)-camphanoyl chloride), to give diastereoisomeric thiol esters which were separated by liquid chromatography, and converted into enantiopure (+)- and (–)-**173** by reductive cleavage. Cyclisation of (+)- and (–)-**173** with acetaldehyde afforded enantiomerically pure *cis/trans* **170a,b** stereoisomers which were separated by HPLC. The sensory properties of **170a,b** stereoisomers are reported in Table 11. Quite

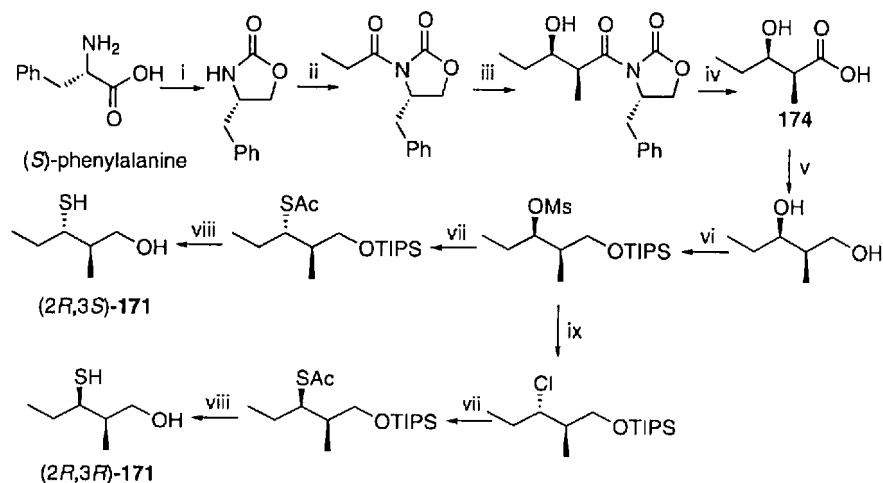
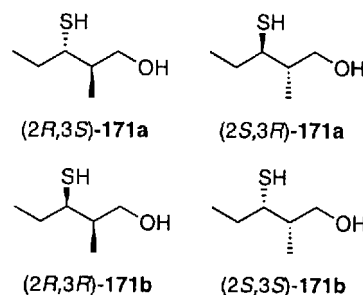
Table 11. Odour properties of oxathianes

Compound	Odour description
(2S,4R)- <b>170a</b>	Fatty, fruity green, tropical fruits, grapefruit
(2R,4S)- <b>170a</b>	Sulphurous, herbaceous green, roasty, linseed oil like, onion
(2R,4R)- <b>170b</b>	Green grass root, earthy red radish note
(2S,4S)- <b>170b</b>	Sulphurous, slight bloomy sweet odour

surprisingly, (2R,4S)-**170a** was then found in a flavour concentrate of fresh yellow passion fruit.<sup>137</sup>

3-Mercapto-2-methylpentanol **171** was identified as a strong aroma component of fresh onions.<sup>138</sup> The four possible stereoisomers (+)- and (–)-**171a** and (+)- and (–)-**171b** were then prepared,<sup>139</sup> in order to determine their sensory properties. The synthetic procedure was based on a diastereoselective aldol reaction, using Evans' benzyloxazolidinone chiral auxiliary. The two enantiomers of hydroxy acid **174** were obtained starting from either (S)- or (R)-phenylalanine.<sup>140</sup> Further derivatisation (Scheme 48) yielded the four enantiopure desired compounds.

All the four isomers showed a *broth-like, sweaty, and leek-like smell*. The perception threshold values were found to strongly depend on the stereochemistry of the odorant. The two *anti* enantiomers **171a** exhibited very low thresholds in water: (2R,3S)-**171a** 0.04 ppb, (2S,3R)-**171a** 0.03 ppb. The thresholds of the *syn* isomers **171b** were higher by factors of 300 and 1000. These latter values could be only roughly estimated, because *syn* derivatives contained trace amounts of the corresponding *anti* isomer.



Scheme 48. Reagents and conditions: (i)  $\text{BF}_3\text{Et}_2\text{O}$ ,  $\text{BH}_3\text{SMe}_2$ ;  $(\text{EtO})_2\text{CO}$ ,  $\text{K}_2\text{CO}_3$ ; (ii) propionyl chloride; (iii)  $\text{Bu}_2\text{BOTf}$ ,  $\text{Et}_3\text{N}$ ;  $\text{EtCHO}$ ; (iv)  $\text{LiOOH}$ ,  $\text{THF}$ ,  $\text{H}_2\text{O}$ ; (v)  $\text{LiAlH}_4$ ; (vi)  $\text{TIPS-Cl}$ ,  $1\text{mH}$ ;  $\text{MsCl}$ ,  $\text{Et}_3\text{N}$ ; (vii)  $\text{KSAc}$ ,  $18\text{-C-6}$ ,  $\text{CH}_3\text{CN}$ ; (viii)  $\text{TBAF}$ ,  $\text{LiAlH}_4$ ; (ix)  $\text{KCl}$ , Aliquat 336,  $\text{H}_2\text{O}$ .

## 6. Lactones

*“But, i’ faith, you have drunk too much canaries;  
and that’s a marvellous searching wine, and it perfumes  
the blood*

*ere one can say ‘What’s this?’ ”*

(W. Shakespeare, King Henry IV Part II, Act II, Scene IV)

$\gamma$ - and  $\delta$ -Lactones are well known naturally occurring chiral flavour compounds. Whereas  $\gamma$ -lactones are important aroma components of many fruits,  $\delta$ -lactones can also be detected in dairy products and other fermented foods.<sup>141</sup> Specific and characteristic enantiomeric ratios have been reported for lactones in apricots, peaches, raspberries, strawberries, plums, mangoes, passion fruit, and juices, wines, and spirit.<sup>29a</sup> (*R*)- $\gamma$ -Decalactone and (*R*)- $\gamma$ -dodecalactone were prevalent in strawberries,<sup>142</sup> and a significant excess of (*R*)- $\gamma$ -decalactone was also detected in raspberry juice.<sup>143</sup> The sensory properties of the enantiomers of a series of  $\gamma$ -lactones were described by Mosandl and Günther.<sup>144</sup> Starting from racemic compounds **175**, 4-hydroxyalkanoic acid isopropyl esters **176** were synthesised by ring opening of the lactone with KOH and alkylation with 2-bromopropane in DMF (Scheme 49). With suitable chiral acyl chlorides, such as (*R*)-2-phenylpropionyl chloride or (1*S*,4*R*)-camphanoyl chloride, diastereoisomeric esters were prepared and separated by LC. Pure diastereoisomers were then hydrolysed and converted into enantiopure  $\gamma$ -lactones **175**, whose sensory properties are reported in Table 12. 4-Alkyl substituted  $\gamma$ -lactone enantiomers exhibit differences in odour quality as well as odour intensity. The (4*R*)-enantiomers are responsible for the pleasant, natural fruity, aroma note. Besides the configuration of the stereogenic carbon atom, even the size of the alkyl side chain plays a key role in sensory activity. (4*R*)- $\gamma$ -Octa, nona, dodecalactones exhibit the highest sensory activity, whereas (4*R*)-pentalactone is less intense (odour threshold 20 ppm). As for 3,4-dimethyl- $\gamma$ -lactone **177a,b**, prepared according to the same procedure, the

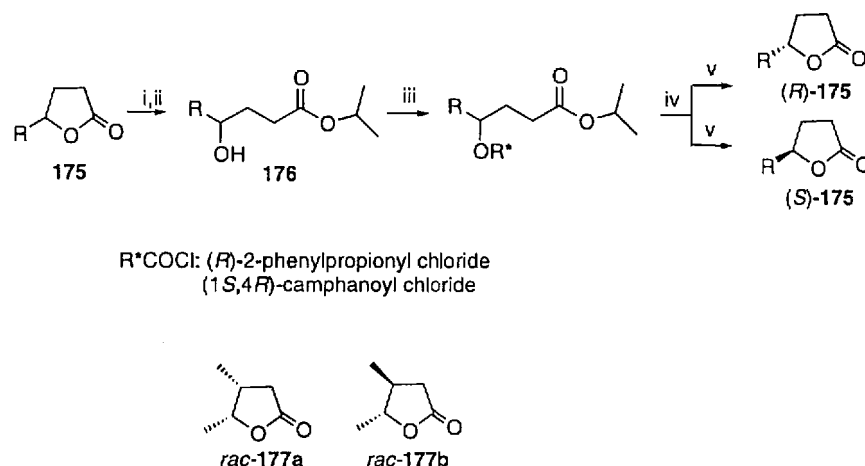
Table 12. Odour properties of lactones **175**

Lactones <b>175</b>	Odour description
$R = C_1$	4 <i>R</i> : faint, sweet 4 <i>S</i> : nearly odourless
$R = C_2$	4 <i>R</i> : faint, sweet coconut with a fatty-herbaceous hay note 4 <i>S</i> : sweet, creamy coconut, with some woody aspects
$R = C_3$	4 <i>R</i> : sweet, spicy, herbaceous hay note, reminiscent of coumarin 4 <i>S</i> : fatty, coconut note, with fruity-sweet aspects, less intense than the enantiomer
$R = C_4$	4 <i>R</i> : spicy-green, coconut note, with almond notes 4 <i>S</i> : fatty, coconut note less intense than the enantiomer
$R = C_5$	4 <i>R</i> : strong, sweet, soft coconut, with fatty-milky aspects 4 <i>S</i> : fatty, mouldy, weak coconut less intense than the enantiomer
$R = C_6$	4 <i>R</i> : strong, fatty-sweet fruity note, some reminiscence to coconut, caramel 4 <i>S</i> : soft, sweet, coconut note with fruity-fatty aspects
$R = C_7$	4 <i>R</i> : strong, fatty-sweet, reminiscent of peach, with some bloomy aspects 4 <i>S</i> : fatty-sweet aldehyde note, less intense than the enantiomer
$R = C_8$	4 <i>R</i> : strong, fruity-sweet, bloomy note with aldehyde and woody aspects 4 <i>S</i> : fatty-fruity, milky note less intense than the enantiomer

(4*S*)-enantiomer is much more intense than the (4*R*)-isomer, both in the *cis* and *trans* series. The odour properties of the enantiomers of **177a** and **177b** are reported in Table 13.

## 6.1. Quercus or whisky lactone

Diastereoisomeric lactones **178a** and **178b** are extracted by wine or other alcoholic beverages like whisky and



**Scheme 49.** Reagents and conditions: (i) KOH, MeOH; (ii) DMF, 2-bromopropane; (iii) R\*COCl, DMAP, CCl<sub>4</sub>; (iv) liquid chromatography; (v) KOH, MeOH; HCl 3N.

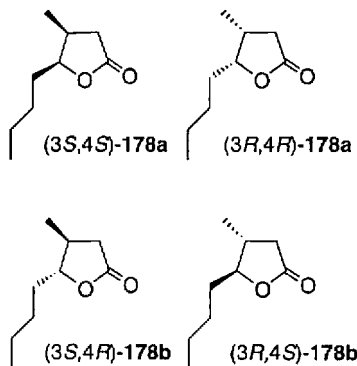
**Table 13.** Odour properties of lactones **177a,b**

Compound	Odour description
(3 <i>R</i> ,4 <i>R</i> )- <b>177a</b>	Faint, sweet hay note
(3 <i>S</i> ,4 <i>S</i> )- <b>177a</b>	Faint, fatty-nutty mouldy note
(3 <i>S</i> ,4 <i>R</i> )- <b>177b</b>	Faint, fatty-spicy note
(3 <i>R</i> ,4 <i>S</i> )- <b>177b</b>	Faint spicy, fatty-fruity note

brandy from oak barrels in which they are kept for maturing. Hence they are nicknamed ‘quercus lactones’ or ‘whisky lactones’. The enantiomeric excesses of natural occurring stereoisomers were 77% for (3*S*,4*S*)-**178a** and 23% for (3*S*,4*R*)-**178b**.<sup>145</sup> The four enantiopure stereoisomers were prepared by Mosandl and Günther according to the same procedure employed for other  $\gamma$ -lactones **175**.<sup>146</sup>

The odour properties of the four enantiopure stereoisomers were the following (evaluated in 10% ethanol solution):

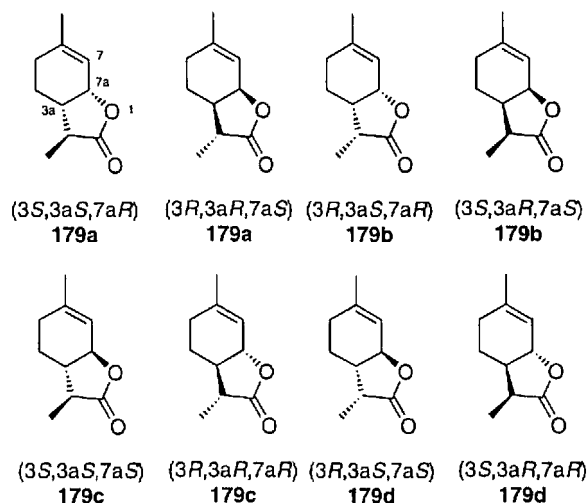
(3*R*,4*R*)-**178a**: sweet, fresh, bright, coconut note  
 (3*S*,4*S*)-**178a**: weak coconut note, earthy, mouldy, afterodor: hay note  
 (3*S*,4*R*)-**178b**: spicy, celery note, weak coconut, distinct green walnut note  
 (3*R*,4*S*)-**178b**: intensive coconut note. Afterodor: reminiscent of celery.



## 6.2. Wine lactone

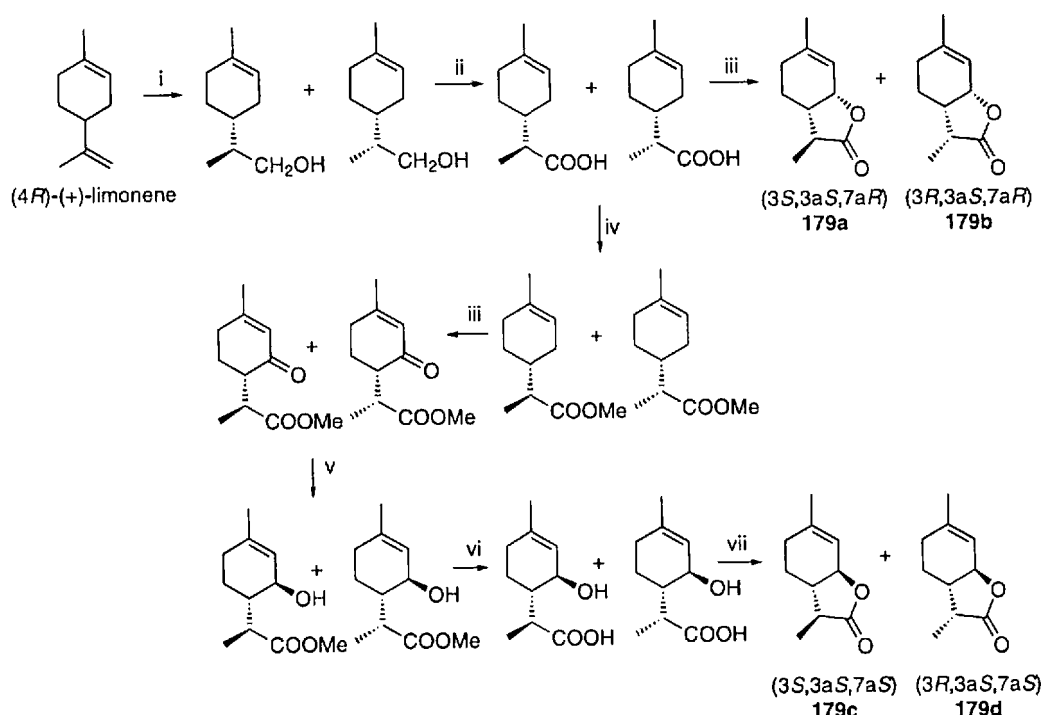
The odorants of different white wines were fully evaluated by Guth.<sup>147</sup> In this work he was able to show that lactone **179** is one of the most relevant flavour compounds. This trace component in wine, showing coconut and sweet odour, is called ‘wine lactone’. It was detected in the past, before the work by Guth, in the excreted urine of koala animals fed with *Eucalyptus punctata*.<sup>148</sup> Guth prepared all the possible eight stereoisomers of lactone **179**, starting from (*S*)- and (*R*)-limonene, according to Scheme 50, in order to determine their threshold values and to ascertain the configuration of natural wine lactone.<sup>149</sup> The threshold

values are reported in Table 14. Low values were found for (3*S*,3*aS*,7*aR*)-**179a**, (3*S*,3*aS*,7*aS*)-**179c**, and (3*S*,3*aR*,7*aR*)-**179d**. The comparison between the two enantiomers of each pair showed that (3*S*)-configuration correlated with a lower threshold. The large differences of the odour threshold values observed (e.g. (3*S*,3*aS*,7*aR*)-**179a** (0.0001 ng/l air) and (3*R*,3*aR*,7*aS*)-**179a** (>1000 ng/l air)) clearly demonstrate that the threshold was significantly influenced by the absolute configuration of the odorant. Natural wine lactone was found to be identical to stereoisomer (3*S*,3*aS*,7*aR*)-**179a**.

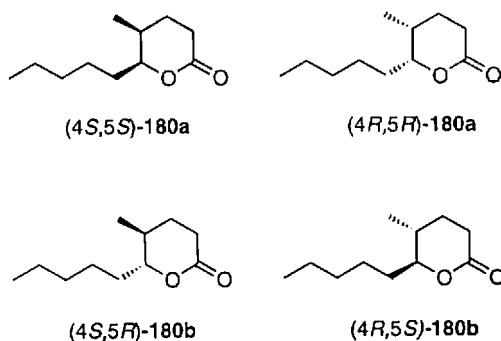


## 6.3. Aerangis lactone

*cis*-Aerangis lactone **180a** (*cis*-4-methyl-5-decanolide) was described by Kaiser in 1993 as the main odour component of the African ‘moth orchids’ *Aerangis confusa* J. Stewart and *Aerangis kirkii* (Rolfe) Schltr.<sup>150</sup> A 1:1 mixture of racemic *cis*-**180a** and racemic *trans*-**180b** was prepared by hydrogenation of dihydrojasnone and subsequent Baeyer–Villiger oxidation.<sup>151</sup> The two diastereoisomers were separated by preparative GC and characterised. The *cis* isomer was found to have a very pleasant and room-filling odour, reminiscent both of the smell of tuberose and gardenia, and of the fragrance of caramel, condensed milk and coconut.<sup>151</sup> The *trans* isomer exhibited similar olfactory properties, but somewhat weaker. In 1995 Mosandl, Kaiser and co-workers<sup>152</sup> obtained all the four stereoisomers of Aerangis lactone, (4*S*,5*S*)- and (4*R*,5*R*)-**180a** and (4*S*,5*R*)- and (4*R*,5*S*)-**180b**, as enantiopure compounds by enantioselective high performance liquid chromatography. By means of enantioselective multidimensional capillary GC the authors found that (4*S*,5*S*)-*cis*-4-methyl-5-decanolide **180a** was the sole stereoisomer of Aerangis lactone present in the scent of living, white flowering orchids (*Aerangis confusa*). The fragrance of (4*S*,5*S*)-**180a** (odour threshold=0.13 ng) was described<sup>152</sup> to be typical for the lactonic odour of *A. confusa* and *A. kirkii*, and identical to the olfactory



**Scheme 50.** Reagents and conditions: (i) 9-BBN, THF; (ii) PDC, DMF; (iii) PDC, benzene, *t*-BuOOH; (iv) MeOH, H<sub>2</sub>SO<sub>4</sub>; (v) NaBH<sub>4</sub>, CaCl<sub>2</sub>, *i*-PrOH; (vi) NaOH, MeOH, H<sub>2</sub>O; (vii) DCC, benzene.



**Table 14.** Odour properties of wine lactone stereoisomers

Compound	Odour threshold (ng/l air)
(3 <i>S</i> ,3 <i>aS</i> ,7 <i>aR</i> )-179a	0.00001–0.00004
(3 <i>R</i> ,3 <i>aR</i> ,7 <i>aS</i> )-179a	> 1000
(3 <i>R</i> ,3 <i>aS</i> ,7 <i>aR</i> )-179b	> 1000
(3 <i>S</i> ,3 <i>aR</i> ,7 <i>aS</i> )-179b	80–160
(3 <i>S</i> ,3 <i>aS</i> ,7 <i>aS</i> )-179c	0.007–0.014
(3 <i>R</i> ,3 <i>aR</i> ,7 <i>aR</i> )-179c	14–28
(3 <i>R</i> ,3 <i>aS</i> ,7 <i>aS</i> )-179d	8–16
(3 <i>S</i> ,3 <i>aR</i> ,7 <i>aR</i> )-179d	0.05–0.2

qualities of natural *Aerangis* lactone. Its enantiomer (4*R*,5*R*)-180a (odour threshold=30.00 ng) was found to be reminiscent of  $\delta$ -decalactone and *cocos*, and with a fragrance intensity much lower than (4*S*,5*S*)-180a. Stereoisomer (4*R*,5*S*)-180b (odour threshold=100.00 ng) showed slightly lactonic fragrances, with the lowest fragrance intensity of all the stereoisomers. The (4*S*,5*R*)-enantiomer (odour threshold=50.00 ng) was reminiscent of  $\delta$ -decalactone and *cocos*, with similar intensity to *cis*-(4*R*,5*R*)-180a and higher than *trans*-(4*R*,5*S*)-180b.

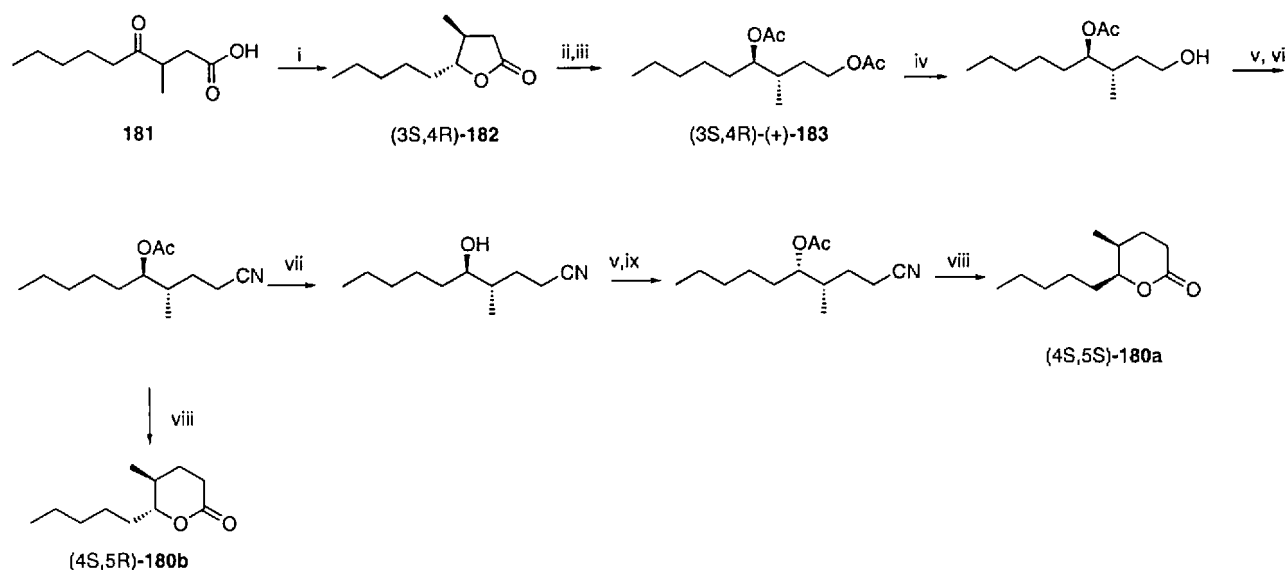
We reported on the first enantioselective synthesis of natural *Aerangis* lactone (–)-180a, and of its epimer (+)-180b, establishing the sign of optical rotation of *Aerangis* lactone isomers.<sup>153</sup> Key steps were the enantiospecific and completely diastereoselective reduction of keto acid 181 mediated by Baker's yeast (BY), to

give cognac lactone (3*S*,4*R*)-182, and the regioselective lipase-catalysed hydrolysis of the primary acetate moiety of derivative (+)-183, followed by suitable chain homologation of one carbon atom via cyanide route, and inversion of the configuration at C(5) (Scheme 51).

## 7. Miscellaneous chiral flavours

εν δε λειμων υποβοτος τεθαλε  
ηρινοισιν ανθειςιν, εν δ' ανητοι  
μελλιχα πνεοισιν  
(Sappho)

"In our meadow where horses graze  
And wild flowers of spring blossom,  
anise shoots fill the air with aroma"  
(translated by Willis Barnstone)



Scheme 51. Reagents and conditions: (i) Baker's yeast; (ii)  $\text{LiAlH}_4$ , THF; (iii)  $\text{Ac}_2\text{O}$ , pyridine; (iv) PPL, THF–water, pH 7.8, NaOH 0.5 M; (v)  $p$ -TsCl, pyridine; (vi) NaCN, DMSO; (vii) KOH, MeOH; (viii) KOH 10%, ethylene glycol; (ix) AcONa, DMF.

Alkyl branched acids and their corresponding esters are well known natural aroma compounds present in fruit and cheese.<sup>142</sup> For example, 2-methylbutanoic acid and its methyl and ethyl esters were detected in apples in enantiopure (*S*)-forms, displaying a sweet and fruity aroma. In contrast, (*R*)-methyl butanoic acid is characterised by a penetrating, cheesy, sweaty odour. 3-Methylpentanoic, 4-methyloctanoic, 4-ethyloctanoic, and 4-methylnonanoic acids were detected in cheese. In all cases the (*S*)-enantiomers have a twofold lower threshold than the (*R*)-enantiomer.<sup>154</sup>

Optically active alkan-2-ols and their acetates are known as key components of the flavour of some foods—for instance, blackberry, corn, coconut, and banana.<sup>155</sup> The enantiomer distribution depends on their origin.<sup>156</sup> Racemic alkan-2-ols were submitted to lipase-catalysed acetylation to obtain resolution.<sup>157</sup> The olfactory properties of the enantiomerically enriched compounds were evaluated and the results are reported in Table 15. Striking differences between the odour qualities of enantiomers can be appreciated.

The first sensory data on 1-octen-3-ol were reported by Mosandl et al.<sup>158</sup> The two enantiomers were prepared by reductive cleavage of diastereoisomeric chiral esters, separated by liquid chromatography. Sensory evaluation was carried out in ethanolic solutions (1%) and gave the following results: (*R*)-(-)-1-octen-3-ol was described *intensive mushroom-like, with a fruity soft odour*; (*S*)-(+)-enantiomer was found *herbaceous, with some reminiscence of mushrooms, but less intensive and not so characteristic in comparison to the (*R*)-enantiomer*. Other optically active 1-alken-3-ols (ee >99%)

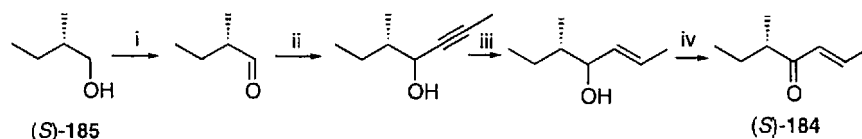
Table 15. Odour properties of alkanols and alkyl acetates

Compound	Odour description
( <i>R</i> )-2-Pentanol	Light, seedy, sharp
( <i>S</i> )-2-Pentanol	Heavy, wild berry, ripe, dusty, astringent
( <i>R</i> )-2-Hexanol	Mushroom, dusty, oily
( <i>S</i> )-2-Hexanol	Mushroom, green, ripe, berry, astringent, metallic
( <i>R</i> )-2-Heptanol	Fruity, sweet, oily, fatty
( <i>S</i> )-2-Heptanol	Mushroom, oily, fatty, blue cheese, mouldy
( <i>R</i> )-2-Octanol	Creamy, cucumber, fatty, sour
( <i>S</i> )-2-Octanol	Mushroom, oily, fatty, creamy, grape
( <i>R</i> )-2-Pentyl acetate	Fruity, Muscat, green, metallic, chemical
( <i>S</i> )-2-Pentyl acetate	Fruity, apple, plum, metallic
( <i>R</i> )-2-Hexyl acetate	Sour, fruity, cherry, plum, strawberry
( <i>S</i> )-2-Hexyl acetate	Sweaty, sour, fruity, plum, nectarine
( <i>R</i> )-2-Heptyl acetate	Green, fatty, banana, methyl ketone
( <i>S</i> )-2-Heptyl acetate	Mushroom, earthy, wild berry
( <i>R</i> )-2-Octyl acetate	Methyl ketone, fatty burnt, boiled vegetable
( <i>S</i> )-2-Octyl acetate	Methyl ketone, fruity, plum, dusty

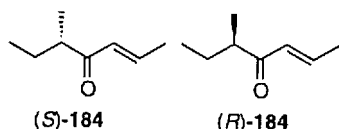
were prepared by enantioselective acylation mediated by lipases.<sup>159</sup> The results of the corresponding sensory evaluation (10% ethanol solution) are reported in Table 16. Most of the panellists involved in the study found that the odour of the (*R*)-isomers was more intense than that of the corresponding (*S*)-enantiomers, and that this difference between the odour strength of the two enantiomers decreased with increasing the number of the carbon atoms in the chain.

Table 16. Odour properties of 1-alken-3-ols

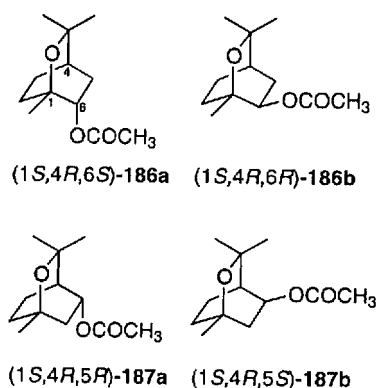
Compound	R-enantiomer	Flavour strength	S-enantiomer
1-Hexen-3-ol	Top impact, acid, meat	>	Metallic, green, earthy
1-Hepten-3-ol	Chemical, diffusible, green	≥	Fruity, earthy
1-Octen-3-ol	Mushroom, fruity	≥	Herbaceous, musty
1-Nonen-3-ol	Mushroom, cheesy, fruity	=	Heavy, metallic, aldehydic
1-Decen-3-ol	Heavy, aldehydic, lactone	=	Metallic, oily, waxy, earthy

Scheme 52. Reagents and conditions: (i)  $K_2Cr_2O_7$ ,  $H_2SO_4$ ,  $H_2O$ ; (ii)  $LiC\equiv CCH_3$ , THF; (iii)  $LiAlH_4$ , THF; (iv)  $MnO_2$ , *n*-pentane.

(*E*)-5-Methylhept-2-en-4-one, filbertone **184**, was isolated<sup>160</sup> from hazelnut extracts and identified as the principal flavour component of filberts (hazelnuts). (*E,S*)-**184** was prepared<sup>161</sup> according to Scheme 52, using (*S*)-(-)-2-methylbutan-1-ol **185** from the chiral pool. Natural filbertone exhibits only a rather low enantiomeric excess, varying with the origin of the hazelnuts: ee = 54.4% (filberts from Turkey), ee = 62.5% (filberts from Italy). The sensory evaluation of (*R*)- and (*S*)-filbertone, separated by chiral GC, established a marked difference between the enantiomers in respect to odour intensity and quality.



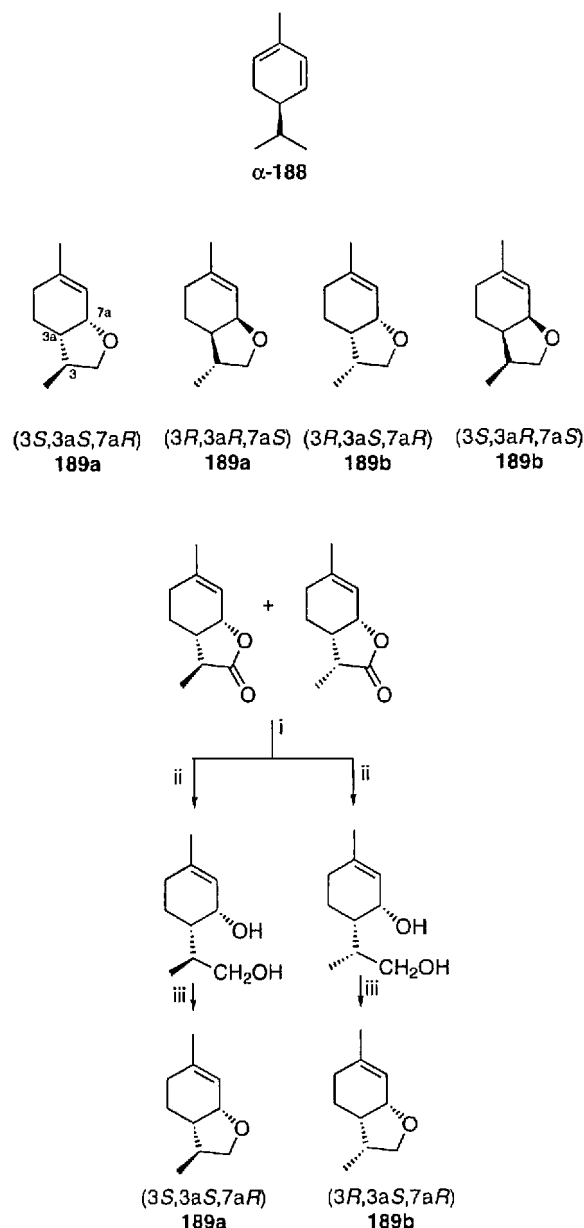
The rhizomes of greater galangal (*Alpinia galanga* Willd.) exhibit a woody, floral, and spicy note which is different from ginger, and they are widely used as a spice throughout Southeast Asia. *trans*- and *cis*-2-Acetoxy-1,8-cineoles **186a** and **186b**, and *trans*- and *cis*-3-acetoxy-1,8-cineoles **187a** and **187b** were identified as natural aroma components of the rhizomes, and they presented individually interesting odours.<sup>162</sup>



The enantiomerically pure acetoxy-1,8-cineols were obtained<sup>163</sup> by preparation of the (*S*)-*O*-methylmandelate esters of the corresponding hydroxy-1,8-cineoles, separation of the resulting diastereoisomers by preparative HPLC, recovery of the enantiopure alcohols by reduction, and subsequent acetylation. The odour evaluations (GC sniffing technique) of the enantiomerically pure samples established that each enantiomer showed a different odour from the other, except for (+)- and (-)-**187a**. In the case of **186a**, the (1*R*,4*S*,6*R*) isomer presented a woody and *A. galanga*-like odour, which was stronger than that of the enantiomer. In addition, the amount of the stronger enantiomer in the rhizomes was about four times more than that of the (1*S*,4*R*,6*S*)-isomer. In the case of **186b**, the (1*R*,4*S*,6*S*) isomer, which was not found in the rhizomes, showed a fruity and sweet odorous note, while the odour of the enantiomer was weak. **187a** was almost optically active in the rhizomes, but the odour of the two enantiomers was very similar, and too weak to be evaluated. **187b** presented a different odour between the two enantiomers (the (1*S*,4*R*,5*S*)-**187b** was camphoraceous, while the (1*R*,4*S*,5*R*) was mild woody), although it might have very little influence on the odour of *A. galanga*, because it is present in the rhizomes in very low concentration. (1*R*,4*S*,6*R*)-**186a** was found to be the most potent odorant of *A. galanga*, both quantitatively and qualitatively.

Dill (*Anethum graveolens* L.) is widely employed as a remedial herb and spice all over the world. The composition of the essential oil differs in various plant parts and changes during the ripening of the dill.<sup>164</sup>  $\alpha$ -Phellandrene **188** and dill ether **189** are the main components in dill herb oil; carvone and limonene in dill seed oil.  $\alpha$ -Phellandrene, dill ether, and carvone are present in enantiopure form in all the plant parts, and during all stages of maturity, whereas both the enantiomers of limonene have been detected<sup>164</sup>. Dill ether is the most important constituent under the organoleptic point of view, and its absolute configuration has been established to be (3*S*,3*aS*,7*aR*).<sup>165</sup> All the eight possible stereoisomers of dill ether were prepared.<sup>166,167</sup> only the

sensory properties of the four *cis* isomers were reported.<sup>166</sup> These latter were prepared using the corresponding four enantiopure stereoisomers of wine lactone as intermediates, via reduction and subsequent cyclisation (Scheme 53). Wine lactones were prepared starting from (+)- and (–)-limonene. By using enantioselective GC/olfactometry the odour characteristics of the stereoisomers were evaluated: (3*S*,3*aS*,7*aR*)-**189a** *dill*; (3*R*,3*aR*,7*aS*)-**189a** *faintly herbal, unspecific*; (3*R*,3*aS*,7*aR*)-**189b** *fruity-sweet*, (3*S*,3*aR*,7*aS*)-**189b** *herbal, sweet*. Only naturally occurring dill ether showed the typical odour of dill oil. Incidentally, it has the same absolute configuration of natural occurring wine lactone. The other stereoisomers showed different, but unspecific odour characteristics.



**Scheme 53.** Reagents and conditions: (i) liquid chromatography; (ii)  $\text{LiAlH}_4$ ; (iii) *p*-TsOH.

## 8. Conclusions

*“Penso com os olhos e com os ouvidos  
e com as mãos e os pés  
e com o nariz e a boca.  
Pensar uma flor è vê-la e cheirá-la  
e comer um fruto è saber-lhe o sentido.”*  
(F. Pessoa, Alberto Caeiro, Poemas Completos,  
O guardador de rebanhos)

“I think with my eyes and with my ears  
And with my hands and feet  
And with my nose and mouth.

Thinking about a flower is seeing and smelling it  
And eating a piece of fruit is tasting its meaning.”

In the aftermath of the September 11th attacks on the World Trade Centre, a ‘weird’ odour persisted in New York City. Air samples in and around Ground Zero were collected and analysed at Monell Chemical Senses Centre in Philadelphia.<sup>168</sup> The presence of acids (acetic acid and nonanoic acid), aldehydes (formaldehyde and benzaldehyde), aromatic hydrocarbons (benzene and styrene), mercaptans, guaiacol, and diethyl phthalate was ascertained. Researchers at Monell were set at work to re-create that smell. The perception of this blend of odorants in a safe environment might help some New Yorkers to overcome September 11th stress, by breaking the association between the odour and the tragic situation where they first smelled it.

This is just one of the most striking implications of odour perception. All chemical senses, and the sense of smell in particular, help us to create our own reality. We like to smell odours, and we cannot imagine a life without them. Recent market research<sup>169</sup> has forecasted a growth for the global demand for flavours and fragrances of 5.4% per year, with the industry reaching \$18.4 billion in 2004. Now, even stereoisomerically enriched odorants have entered the market: *Hedione* HC®, *Dextro-norlimbanol*®, *Bacdanol*®. The investigation of the main odour vector of stereoisomeric odorants is not merely academic, but it has important social and economical implications.

One of the basic laws of chemistry is that *only chiral means are able to distinguish chiral objects*. Human beings are themselves chiral, so it is not surprising that they can recognise enantiomers. The extent of this recognition varies according to the effectiveness of the interaction between the odorous molecule and our chiral receptors. There are examples of enantiomers which cannot be discriminated by human nose, as well as there are reactions involving chiral reagents or auxiliaries that unluckily proceed without enantioselectivity. Thus, enantiodifferentiation is probably observed when the portion of the molecule containing the stereogenic elements is offered to the receptor site. It is interesting to notice that for structurally related odorants the

absolute configuration of the main odour vector is similar, thus confirming the existence of a correlation between spatial disposition of substituents and the quality of interaction. Suitable examples are derivatives of campholenic aldehydes, rose oxide versus Dore-mox<sup>®</sup>, Floropal<sup>®</sup> versus Magnolan<sup>®</sup>, dill ether versus wine lactone.

Frater and Kraft<sup>71</sup> made the following considerations on the enantioselectivity of odour perception: (i) if both enantiomers possess similar odour thresholds, it is probable that the stereogenic elements are located in the hydrophobic bulk region of the odorant, the geometry of which is of no influence in the process of odour recognition; (ii) when the stereogenic elements are located in the profile region, that is to say in the portion of the molecule fitting the binding side of the receptor, then one enantiomer is usually odourless, the other one has a very low odour threshold; (iii) if there are no examples of enantioselectivity for a certain class of odorants, it is likely that the most potent odorant of that family has not been discovered yet.<sup>170</sup> Thus, by placing stereogenic elements in different portions of the molecule it would be possible to detect the bulk region and the profile site of a certain odorant.

These considerations underline the importance of the investigation of the odour properties of enantiomers. Reliable sensory data can be collected only by using isolated samples with high values of enantiomeric excess. These requirements imply that the investigation of highly stereoselective synthetic methods and the optimisation of effective analytical techniques for enantiomer separation and characterisation are needed. The chemical nature of flavours and fragrances is so different that almost any kind of optical activation methods has been exploited: classical resolution via separation of diastereoisomers; stereoselective synthesis employing chiral compounds from the 'chiral pool'; catalytic stereoselective synthesis; enzyme-mediated transformations; lipase-mediated kinetic resolution. The challenge of investigating the odour active isomers of chiral odorants is highly stimulating, and it is addressed to the whole community of organic chemists.

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